Douglas S. Eakeley
Jason Halper
LOWENSTEIN SANDLER PC
Attorneys at Law
65 Livingston Avenue
Roseland, New Jersey 07068
(973) 597-2500

Donald A. Robinson
ROBINSON WETTRE & MILLER LLC
One Newark Center, 19th Floor
Newark, New Jersey 07102
(973) 690-5400

Attorneys for Plaintiffs
Schering Corporation and MSP Singapore Company LLC

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

SCHERING CORPORATION, and MSP SINGAPORE COMPANY LLC, Plaintiff, v. TEVA PHARMACEUTICALS USA, INC. and TEVA PHARMACEUTICAL INDUSTRIES LTD. Defendants.	Civil Action No. _____ **COMPLAINT**

Plaintiffs Schering Corporation and MSP Singapore Company, LLC (collectively "Plaintiffs"), by their attorneys, hereby allege as follows:

NATURE OF THE ACTION

1. This is an action for patent infringement under the patent laws of the United States, Title 35, United States Code, that arises out of the filing by Defendant Teva Pharmaceuticals USA, Inc. of Abbreviated New Drug Application ("ANDA") No. 200-909 with

the U.S. Food and Drug Administration ("FDA") seeking approval to manufacture and sell a generic version of Vytorin® (ezetimibe/simvastatin tablets, 10mg/80mg) prior to the expiration of U.S. Patent No. RE37,721 and U.S. Patent No. 5,846,966.

PARTIES

2. Plaintiff Schering Corporation is a corporation organized and existing under the laws of the State of New Jersey, with its principal place of business at 2000 Galloping Hill Road, Kenilworth, New Jersey 07033.

3. Plaintiff MSP Singapore Company LLC is a company organized and existing under the laws of the State of Delaware, with a place of business at 2000 Galloping Hill Road, Kenilworth, New Jersey 07033.

4. Schering Corporation and MSP Singapore Company LLC are both owned, directly or indirectly, by Merck & Co., Inc.

5. On information and belief, Defendant Teva Pharmaceuticals USA, Inc. ("Teva USA") is a corporation organized under the laws of Delaware having its principal place of business at 1090 Horsham Road, North Wales, Pennsylvania 19454.

6. On information and belief, Defendant Teva Pharmaceutical Industries Ltd. ("Teva Ltd.") is a company organized and existing under the laws of Israel with its principal place of business at 5 Basel St. Petach Tikva 49131, Israel.

7. On information and belief, Teva USA is a wholly owned subsidiary of Teva Ltd.

8. On information and belief, Teva USA's preparation and submission of ANDA No. 200-909 was done collaboratively with, and at least in part for the benefit of, Teva Ltd.

9. Teva USA and Teva Ltd. hereinafter are referred to collectively as "Teva."

10. Teva manufactures and sells various generic drug products and regularly conducts business throughout the United States, including in the State of New Jersey.

JURISDICTION AND VENUE

11. This is an action for patent infringement, arising under 35 U.S.C. § 1 et seq. generally, and 35 U.S.C. § 271(e)(2) specifically.

12. This Court has subject matter jurisdiction over this dispute pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

13. Venue is proper in this Court pursuant to 28 U.S.C. §§ 1391 and 1400(b).

14. This Court has personal jurisdiction over each of the Defendants by virtue of the fact that, *inter alia*, each Defendant has committed, or aided, abetted, contributed to and/or participated in the commission of, a tortious act of patent infringement that has led to foreseeable harm and injury to a New Jersey corporation, Plaintiff Schering Corporation, in New Jersey. This Court has personal jurisdiction over each of the Defendants for the additional reasons set forth below and for other reasons that will be presented to the Court if such jurisdiction is challenged.

15. On information and belief, Teva USA is in the business of formulating, manufacturing, marketing, and selling generic prescription pharmaceutical drugs that it distributes in New Jersey and throughout the United States. On information and belief, Teva USA is registered to do business in New Jersey and engages in continuous and systematic contacts with New Jersey.

16. On information and belief, Teva Ltd, directly or through Teva USA, is in the business of formulating, manufacturing, marketing, and selling generic prescription

pharmaceutical drugs that it distributes in New Jersey and throughout the United States. Such business activities by Teva Ltd. include, but are not limited to, Teva Ltd.'s direction of the operations and management of Teva USA inclusive of Teva USA's New Jersey facilities and the shipment of drugs to Teva USA from locations outside the United States for distribution by Teva USA within the United States generally, and New Jersey specifically.

17. On information and belief, Teva USA acts under the direction, control, and influence of Teva Ltd. with respect to, at least, the acts and conduct alleged in this Complaint.

18. Teva USA's acts and continuous and systematic contacts with the State of New Jersey, as an agent of Teva Ltd., are also attributable to Teva Ltd. for jurisdictional purposes.

19. On information and belief, Teva Ltd. and Teva USA have jointly filed numerous complaints in this judicial district in the last five years, including patent infringement cases, and therefore, have submitted themselves to the jurisdiction of this Court and availed themselves of the laws and protections of New Jersey. These cases include, but are not limited to: *Teva Pharm. Indus. Ltd. et al. v. Glenmark Generics Inc., USA et al.*, Civ. A. No. 3:08-cv-04355 (GEB/DEA), filed August 29, 2008; *Teva Pharm. Indus. Ltd. et al. v. Apotex, Inc. et al.*, Civ. A. No. 3:07-cv-05514 (GEB/JJH), filed November 15, 2007; *Teva Pharm. Indus. Ltd. et al. v. Zydus Pharms., Inc. et al.*, Civ. A. No. 3:07-cv-0942 (GEB/TJB), filed October 12, 2007; *Teva Pharm. Indus. Ltd. et al. v. Dr. Reddy's Labs., Ltd.*, Civ. A. No. 3:07-cv-02894 (GEB/JJH), filed June 21, 2007; *Teva Pharm. Indus. Ltd. et al. v. Cobalt Pharms., Inc. et al.*, Civ. A. No. 2:07-cv-04214 (WHW-CCC), filed April 10, 2007.

20. This Court has personal jurisdiction over Teva USA by virtue of, among other things, (1) its presence in New Jersey; (2) its registration to do business in New Jersey, including its appointment of a registered agent in New Jersey (located at 811 Church Road, Suite 150, Cherry Hill, NJ 08002) for the receipt of service of process; (3) its sale of a substantial volume of prescription drugs in New Jersey; (4) its filing of lawsuits in New Jersey; (5) its continuous and systematic contacts with New Jersey; and (6) its course of conduct that is designed to cause the performance of tortious acts that will result in foreseeable harm in New Jersey.

21. This Court has personal jurisdiction over Teva Ltd. by virtue of, among other things, (1) its presence in New Jersey; (2) its sale of a substantial volume of prescription drugs in New Jersey; (3) its filing of lawsuits in New Jersey; (4) its continuous and systematic contacts with New Jersey; and (5) its course of conduct that is designed to cause the performance of tortious acts that will result in foreseeable harm in New Jersey.

BACKGROUND

22. Vytorin® contains ezetimibe (a cholesterol absorption inhibitor) and simvastatin (a HMG-CoA reductase inhibitor (statin)). According to its approved label, Vytorin® "is indicated for the reduction of elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and non-high density lipoprotein cholesterol (non-HDL-C), and to increase high-density lipoprotein cholesterol (HDL-C) in patients with primary (heterozygous familial and non-familial) hyperlipidemia or mixed hyperlipidemia." Vytorin® is also "indicated for the reduction of elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable."

23. Plaintiffs sell Vytorin® in the United States pursuant to a New Drug Application that has been approved by the FDA.

CLAIM

(INFRINGEMENT OF U.S. PATENT NO. RE37,721 AND U.S. PATENT NO. 5,846,966)

24. Plaintiffs incorporate each of the preceding paragraphs 1-23 as if fully stated herein.

25. On May 28, 2002, the United States Patent and Trademark Office issued U.S. Patent No. RE37,721 (the " '721 Patent") to Schering Corporation. A true and correct copy of the '721 Patent is attached hereto as **Exhibit A**.

26. Schering Corporation is the assignee of the '721 Patent. MSP Singapore Company LLC is the exclusive licensee of Schering Corporation for the product Vytorin®, the drug covered by FDA-approved New Drug Application ("NDA") No. 21-687. One of the active ingredients in Vytorin® is ezetimibe, which is an embodiment of the '721 Patent claims.

27. Plaintiffs own all rights, title and interest in the '721 Patent, including all rights needed to bring this action in Plaintiffs' own names.

28. Vytorin® is covered by one or more claims of the '721 Patent, and the '721 Patent has been listed in connection with Vytorin® in the FDA's publication, *Approved Drug Products with Therapeutic Equivalence Evaluations*, which is referred to as the "Orange Book," as a patent "with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug" Vytorin®.

29. On December 8, 1998, the United States Patent and Trademark Office issued U.S. Patent No. 5,846,966 (the " '966 Patent") to Schering Corporation. A true and correct copy of the '966 Patent is attached hereto as **Exhibit B**.

30. Schering Corporation is the assignee of the '966 Patent. MSP Singapore Company LLC is the exclusive licensee of Schering Corporation for the product Vytorin®, the drug covered by FDA-approved New Drug Application ("NDA") No. 21-687. The active ingredients in Vytorin® are a combination of simvastatin and ezetimibe, and this combination is an embodiment of the '966 Patent claims.

31. Plaintiffs own all rights, title and interest in the '966 Patent, including all rights needed to bring this action in Plaintiffs' own names.

32. Vytorin® is covered by one or more claims of the '966 Patent, and the '966 Patent has been listed in connection with Vytorin® in the FDA's publication, *Approved Drug Products with Therapeutic Equivalence Evaluations*, which is referred to as the "Orange Book," as a patent "with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug" Vytorin®.

33. By letter dated February 19, 2010 (the "Notice Letter"), Teva USA notified Plaintiffs that it had submitted to the FDA ANDA No. 200-909, for Teva's ezetimibe/simvastatin 10 mg/80 mg tablets, a drug product that is a generic version of Vytorin® ("Teva's ANDA Product"). The purpose of the submission of the ANDA was to obtain permission under the Federal Food, Drug, and Cosmetic Act ("FDCA") to engage in the commercial manufacture, use, offer for sale, and/or sale of Teva's ANDA Product prior to the

expiration of the '966 and '721 Patents. Plaintiffs received the Notice Letter on February 22, 2010.

34. This action is being commenced before the expiration of forty-five days from the date of the Notice Letter.

35. In the Notice Letter, Teva USA also notified Plaintiffs that, as a part of its ANDA, Teva USA had filed certifications of the type described in Section 505(j)(2)(A)(vii)(IV) of the FDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV), with respect to the '966 and '721 Patents. Upon information and belief, Teva USA submitted ANDA No. 200-909 to the FDA containing a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) asserting that the '966 and '721 Patents are invalid, unenforceable, and/or will not be infringed by the manufacture, use, offer for sale, or sale of Teva's ANDA Product.

36. The use of Teva's ANDA Product is covered by one or more claims in each of the '966 and '721 Patents.

37. Teva had knowledge of the '966 and '721 Patents when it submitted ANDA No. 200-909.

38. Teva USA's filing of ANDA No. 200-909 for the purpose of obtaining approval to engage in the commercial manufacture, use, offer for sale, and/or sale of Teva's ANDA Product before the expiration date of the '966 and '721 Patents is an act of infringement of the '966 and '721 Patents, under 35 U.S.C. § 271(e)(2).

39. The commercial manufacture, use, offer for sale, sale, marketing, distributing, and/or importation of Teva's ANDA Product would infringe one or more claims in each of the '966 and '721 Patents.

40. Upon information and belief, the use of Teva's ANDA Product in accordance with and as directed by Teva's proposed labeling for that product would infringe one or more claims in each of the '966 and '721 Patents.

41. On information and belief, unless enjoined by this Court, Teva intends to engage in the manufacture, use, offer for sale, sale, marketing, distributing, and/or importation of Teva's ANDA Product with its proposed labeling immediately and imminently upon approval of ANDA No. 200-909.

42. On information and belief, unless enjoined by this Court, Teva plans and intends to, and will, actively induce infringement of the '966 and '721 Patents when its ANDA No. 200-909 is approved, and plans and intends to, and will, do so immediately and imminently upon approval.

43. On information and belief, Teva knows that Teva's ANDA Product and its proposed labeling are especially made or adapted for use in infringing the '966 and '721 Patents, and that Teva's ANDA Product and its proposed labeling are not suitable for substantial noninfringing use. On information and belief, unless enjoined by this Court, Teva plans and intends to, and will, contribute to the infringement of the '966 and '721 Patents immediately and imminently upon approval of ANDA No. 200-909.

44. The foregoing actions by Teva constitute and/or will constitute infringement of the '966 and '721 Patents, active inducement of infringement of the '966 and '721 Patents, and/or contribution to the infringement by others of the '966 and '721 Patents.

45. On information and belief, Teva acted without a reasonable basis for believing that it would not be liable for infringing the '966 and '721 Patents, actively inducing

infringement of the '966 and '721 Patents, and/or contributing to the infringement by others of the '966 and '721 Patents.

46. Unless Teva is enjoined from infringing the '966 and '721 Patents, actively inducing infringement of the '966 and '721 Patents, and/or contributing to the infringement of the '966 and '721 Patents, Plaintiffs will suffer irreparable injury.

47. Plaintiffs are entitled to the relief provided by 35 U.S.C. § 271(e)(4), including, *inter alia*, an order of this Court that the FDA set the effective date of approval for Teva USA's ANDA to be a date which is not earlier than April 25, 2017, the expiration date of the '721 Patent. (The '966 Patent expires on March 21, 2014.)

48. Plaintiffs do not have an adequate remedy at law.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs pray that this Court grant the following relief:

A. A declaration that the '966 and '721 Patents are valid and enforceable.

B. A judgment that the '966 and '721 Patents would be infringed by Teva's ANDA Product; that submission of ANDA No. 200-909 is an act of infringement of the '966 and '721 Patents; and that Teva's making, using, offering to sell, selling, marketing, distributing, or importing Teva's ANDA Product, or any product or compound that infringes the '966 and '721 Patents, prior to the expiration dates of the '966 and '721 Patents, would infringe, actively induce infringement, and contribute to the infringement of the '966 and '721 Patents.

C. An Order pursuant to 35 U.S.C. § 271(e)(4) providing that the effective date of any FDA approval of Teva's ANDA No. 200-909, or any product or compound that infringes the '966 and '721 Patents, shall be a date which is not earlier than April 25, 2017, the expiration date of the '721 Patent (the '966 Patent expires on March 21, 2014);

D. An Order permanently enjoining Teva, and its affiliates and subsidiaries, and each of their officers, agents, servants and employees, from making, using, offering to sell, selling, marketing, distributing, or importing Teva's ANDA Product, or any other product or compound, not colorably different, that infringes the '966 and '721 Patents, or inducing or contributing to the infringement of the '966 and '721 Patents until after the expiration of the '966 and '721 Patents;

E. Damages or other monetary relief, including prejudgment interest, if Teva engages in the commercial manufacture, use, offer to sell, sale, marketing, distribution, or importation of Teva's ANDA Product, or any product or compound that infringes the '966 and '721 Patents, or the inducement or contribution of the foregoing, prior to the expiration of the '966 and '721 Patents.

F. A declaration that this is an exceptional case and an award of attorneys' fees to Plaintiffs pursuant to 35 U.S.C. §§ 271(e)(4) and 285;

G. Plaintiffs' reasonable costs of suit incurred; and

H. Such other and further relief as this Court may deem just and proper.

Dated: March 2, 2010

Respectfully submitted,

Douglas S. Eakeley
Jason Halper
LOWENSTEIN SANDLER
Attorneys at Law
65 Livingston Avenue
Roseland, New Jersey 07068
(973) 597-2500
(973) 597-2400 (Fax)
jhalper@lowenstein.com

Donald A. Robinson
ROBINSON WETTRE & MILLER LLC
One Newark Center, 19th Floor
Newark, New Jersey 07102
(973) 690-5400
(973) 466-2760 (Fax)
drobinson@RWMLegal.com

Attorneys for Plaintiffs
Schering Corporation and
MSP Singapore Company LLC

By: /s Jason Halper
Jason Halper

Of Counsel:

David T. Pritikin
William H. Baugmartner, Jr.
Sidley Austin LLP
1 S. Dearborn Street
Chicago, Illinois 60603
(312) 853-7000
(312) 853-7036 (Fax)
dpritikin@sidley.com

- and-

Todd L. Krause
Sidley Austin LLP
787 Seventh Avenue
New York, New York 10019
(212) 839-5300
(212) 839-5599 (Fax)
tkrause@sidley.com

LOCAL CIVIL RULE 11.2 CERTIFICATION

The undersigned hereby certifies that the underlying events at issue in this case are also the subject of the following actions that have been filed in the District of New Jersey: (1) Schering Corporation, et al. v. Glenmark Pharmaceuticals Inc., et al., Civil Action No. 07-1334 (JLL) (ES); and (2) Schering Corporation, et al. v. Mylan Pharmaceuticals Inc., et al., Civil Action No. 09-6383 (JLL) (ES). Both of those cases, and this action, involve Hatch-Waxman patent infringement claims filed by the same plaintiffs. The Glenmark matter (07-1334) involves one of the patents (U.S. Patent No. RE37,721) asserted in this case, and the Mylan matter (09-6383) involves both of the patents (U.S. Patent No. RE37,721 and U.S. Patent No. 5,846,966) asserted in this case. This case is therefore related to the Glenmark and Mylan matters, and both the Glenmark and Mylan matters have been assigned to the Honorable Jose L. Linares, U.S.D.J. and the Honorable Esther Salas, U.S.M.J. The matter in controversy is not the subject of any pending arbitration or administrative proceeding.

Dated: March 2, 2010

By: __/s Jason Halper_____
Jason Halper

Exhibit A

US00RE37721E

(19) **United States**

(12) **Reissued Patent**

Rosenblum et al.

(10) **Patent Number: US RE37,721 E**

(45) **Date of Reissued Patent: May 28, 2002**

(54) **HYDROXY-SUBSTITUTED AZETIDINONE COMPOUNDS USEFUL AS HYPOCHOLESTEROLEMIC AGENTS**

(75) Inventors: **Stuart B. Rosenblum**, West Orange; **Sundeep Dugar**, Bridgewater; **Duane A. Burnett**, Fanwood; **John W. Clader**, Cranford; **Brian A. McKittrick**, Bloomfield, all of NJ (US)

(73) Assignee: **Schering Corporation**, Kenilworth, NJ (US)

(21) Appl. No.: **09/594,996**

(22) Filed: **Jun. 15, 2000**

Related U.S. Patent Documents

Reissue of:

(64) Patent No.: **5,767,115**
Issued: **Jun. 16, 1998**
Appl. No.: **08/617,751**
Filed: **Mar. 18, 1996**

U.S. Applications:

(63) Continuation-in-part of application No. 08/257,593, filed on Jun. 9, 1994, now Pat. No. 5,631,365, which is a continuation-in-part of application No. 08/102,440, filed on Sep. 21, 1993, now abandoned.

(51) **Int. Cl.**[7] **C07D 205/08**; A61K 31/395; A61P 9/10; A61P 3/06

(52) **U.S. Cl.** **514/210**; 540/200

(58) **Field of Search** 514/210; 540/200

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,144,232 A	3/1979	Koppel et al.	260/239 A
4,375,475 A	3/1983	Willard et al.	424/279
4,443,372 A	4/1984	Luo et al.	260/239 A

(List continued on next page.)

FOREIGN PATENT DOCUMENTS

DE	2046823	3/1972
EP	0 199 630 A1	10/1986
EP	0 264 231 A1	4/1988
EP	0 333 268 A1	9/1989
EP	0337 549 A1	10/1989
EP	0 365 364 A2	4/1990
EP	0 415 487 A2	3/1991
EP	0 462 667 A2	12/1991
EP	0 481 671 A1	4/1992
EP	0 524 595 A1	1/1993
WO	WO 87/04429	7/1987
WO	WO 93/02048	2/1993
WO	WO 94/17038	8/1994

OTHER PUBLICATIONS

Simova, E. "Aldol-type addition of hydrocinnamic acid esters to benzylidencaniline", Chemical Abstracts No. 15, vol. 86, Apr. 11, 1977, Abstract 106130h.

Otto et al., Stereochemistry of dehydration and halogenation of αR* and αS* isomeric 3-(α-hydroxybenzyl)-1, 4-diphenyl=2-azetidinones, Chemical Abstracts No. 19, vol. 99, Nov. 7 1983 abstract 158083h.

Nobuki, O. et al. "Stereoselective syntheses of β-lactam derivatives by ultrasound promoted Reformatskii reaction" Chemical Abstracts No. 106, vol. 17, Apr. 27, 1977 abstract 138174y.

T. Durst et al., 1971, "Metallation of N-Substituted β-Lactams. A Method for the Introduction of 3-Substituents into β-Lactams" *Canadian Journal of Chemistry*, 50:3196-3201.

C. Allain et al., 1974, "Enzymatic Determination of Total Serum Cholesterol" *Clinical Chemical*, 20:470-475.

R. Mayrhofer et al. 1980, "Simple Preparation of 3-Benzylidene-2-azetilidinones" *Synthesis*, 247-248.

M. Hoekman et al., 1982, "Synthesis of Homologues of 4,5-Dihydroxy- and 4-Hydroxy-5-oxohexanoic Acid$_\delta$-Lactones", *J. Agric. Food Chem.*, 30:920-924.

H. Otto et al., 1983, "Darstellung und Stereochemie von 3-(α-Hydroxybenzyl)-1,4-diphenyl-2-azetidononen", *Liebigs Ann. Chem.* 1152-1161.

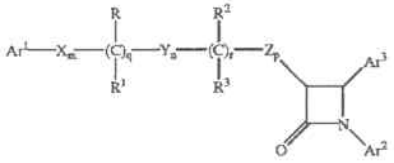
(List continued on next page.)

Primary Examiner—Mark L. Berch

(74) *Attorney, Agent, or Firm*—Richard C. Komson; Dorothy R. Auth; Morgan & Finnegan, L.L.P.

(57) **ABSTRACT**

Hydroxy-substituted azetidinone hypocholesterolemic agents of the formula



or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 and Ar^2 are aryl or R^4-substituted aryl;

Ar^3 is aryl or R^5-substituted aryl;

X, Y and Z are $—CH_2—$, —CH(lower alkyl)— or —C(dilower alkyl)—;

R and R^2 are $—OR^6$, $—O(CO)R^6$, $—O(CO)OR^9$ or $—O(CO)NR^6R^7$;

R^1 and R^3 are H or lower alkyl;

q is 0 or 1; r is 0 or 1; m, n and p are 0-4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1-6; and provided that when p is O and r is 1, the sum of m, q and n is 1-5;

R^4 is selected from lower alkyl, R_5, $—CF_3$, —CN, $—NO_2$ and halogen R^5 is selected from $—OR^6$, $—O(CO)R^6$, $—O(CO)OR^9$, $—O(CH_2)_{1-5}OR^6$, $—O(CO)NR^6R^7$, $—NR_5R^7$, $—NR^6(CO)R^7$, $—NR^6(CO)OR^9$, $—NR^6(CO)NR^7R^8$, $—NR^6SO_2R^9$, $—COOR^6$, $—CONR^6R^7$, $—COR^6$, $—SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $—O(CH_2)_{1-10}—COOR^6$, $—O(CH_2)_{1-10}CONR^6R^7$, —(lower alkylene)$COOR^6$ and —CH=CH—$COOR^6$;

R^6, R^7 and R^8 are H, lower alkyl or aryl-substituted Ic

R^9 is lower alkyl, aryl or aryl-substituted lower alkyl;

are disclosed, as well as a method of lowering serum cholesterol by administering said compounds, alone or in combination with a cholesterol biosynthesis inhibitor, pharmaceutical compositions containing them; and a process for preparing them.

13 Claims, No Drawings

U.S. PATENT DOCUMENTS

4,479,900	A	10/1984	Luo	260/239 A
4,500,456	A	2/1985	Spitzer et al.	260/239 A
4,576,749	A	3/1986	Zahler et al.	260/239 A
4,576,753	A	3/1986	Kamiya et al.	260/239 A
4,595,532	A	6/1986	Miller	260/239 A
4,620,867	A	11/1986	Luo	260/239 A
4,633,017	A	12/1986	Mueller et al.	564/301
4,675,399	A	6/1987	Miller	540/355
4,680,391	A	7/1987	Firestone et al.	540/355
4,784,734	A	11/1988	Torii et al.	204/81
4,794,108	A	12/1988	Kishimoto et al.	514/210
4,803,266	A	2/1989	Kawashima et al.	540/200
4,834,846	A	5/1989	Abramson et al.	204/59 R
4,876,365	A	10/1989	Kirkup et al.	549/215
4,983,597	A	1/1991	Yang et al.	540/200
5,030,628	A	7/1991	Joyeau et al.	514/210
5,099,034	A	3/1992	Yoshida et al.	549/265
5,120,729	A	6/1992	Chabala et al.	514/210
5,229,381	A	7/1993	Doherty et al.	514/210
5,229,510	A	7/1993	Knight et al.	540/360
5,306,817	A	4/1994	Thiruvengadam et al.	540/200
5,348,953	A	9/1994	Doherty et al.	514/210
5,350,868	A	9/1994	Yoshida et al.	554/154
5,412,092	A	5/1995	Rey et al.	540/200
5,550,229	A	8/1996	Iwasaki et al.	540/200
5,661,145	A	8/1997	Davis	514/210
5,688,785	A	11/1997	Vaccaro	540/200
5,688,787	A	11/1997	Burnette et al.	540/200
5,688,990	A	11/1997	Shankar	560/39
5,728,827	A	3/1998	Thiruvengadam et al.	540/200
5,739,321	A *	4/1998	Wu	540/200
5,817,806	A	10/1998	Rossi et al.	540/200
5,847,115	A	12/1998	Iwasaki et al.	540/200
5,856,473	A *	1/1999	Shankar	540/200

OTHER PUBLICATIONS

G. George et al., 1985 "3-(1'-Hydroxyethyl)-2-Azetidinones From 3-Hydroxybutyrates and N-Arylaldimines" *Tetrahedron Letters*, vol. 26, No. 33 pp. 3903–3906.

Hart et al., 1985 "An Enantioselective Approach to Carbapenen Antibodies: Formal Synthesis of (+)-Thienamycin" *Tetrahedron Letters*, vol. 26, No. 45 pp. 5493–5496.

Panfil. I. et al., 1986, "Synthesis of β-Lactams from α, β-Unsaturated Sugar δ-Lactones" *Heterocycles* 24:1609–1617.

D. Roger Illingworth, 1988, "An Overview of Lipid-Lower Drugs" *Drugs* 36:63:71.

Joseph L. Witztum, M.D., 1989, "CUrrent Approaches to Drug Therapy for the Hyercholesterolemic Patient" *Circulation* 80:1101–1114.

B. Ram et al., 1990, "Potential hypolipidemic agents:Part V†-Synthesis biological activity of new ethyl 4-(2-oxoazetidin-4-yl)phenoxyalkanoates‡" *Indian Journal of Chemistry* 29B:1134–1137.

Schnitzer-Polokoff, R. et al. 1991, "Effects of Acyl-CoA: Cholesterol O-Acyltransferase Inhibition on Cholesterol Absorption and Plasma Lipoprotein Composition in Hamsters" *Comp. Biochem. Physiol.* 99A:665–670.

Horie, M. et al. 1991, "Hypolipidemic effects of NB-598 in dogs" *Atherosclerosis* 88:183–192.

Baxter, A., 1992, "Squalestatin 1, a Potent Inhibitor of Squalene Synthase, Which Lowers Serum Cholesterol in Vivo," *The Journal of Biological Chemistry* 267:11705–11708.

Summary Factfile, May 1992, "Anti-Atherosclerotic Agents" Current Drugs Ltd. pp. A5–A23.

Harwood, H. James, 1993, "Pharmacologic consequences of cholesterol absorption inhibition: alteration in cholesterol metabolism and reduction in plasma cholesterol concentration induced by the synthetic saponin β-tigogenin cellobioside (CP-88818;tiqueside)[1]" *Journal of Lipid Research* 34:377–395.

Salisbury, B. et al., 1995, "Hypocholesterolemic activity of a novel inhibitor of cholesterol absorption, SCH 48461" *Atherosclerosis* 115:45–63.

Burrier, R.E. et al., 1994, "Demonstration of a Direct Effect on Hepatic Acyl CoA:Cholesterol Acyl Transferase (ACAT) Activity By An Orally Administered Enzyme Inhibitor in the Hamster", *Biochemical Pharmacology* 47:1545–1551.

Burrier, R.E. et al., 1994, "The Effect of Acyl CoA:Cholesterol Acyltransferase Inhibition on the Uptake, Esterification and Secretion of Cholesterol by the Hamster Small Intestine", *The Journal of Pharmacology and Experimental Therapeutics* 272:156–163.

Clader, J.W. et al., 1995, "Substituted (1,2-Diarylethyl)amide Acyl-CoA:Cholesterol Acyltransferase Inhibitors: Effect of Polar Groups in Vitro and in Vivo Activity" *Journal of Medicinal Chemistry* 38:1600–1607.

Sybertz, E. 1995, "SCH 48461, a novel inhibitor of cholesterol absorption" *Atherosclerosis* pp. 311–315.

* cited by examiner

HYDROXY-SUBSTITUTED AZETIDINONE COMPOUNDS USEFUL AS HYPOCHOLESTEROLEMIC AGENTS

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

The present application is the United States national application corresponding to International Application No. PCT/US94/10099, filed Sep. 14, 1994 and designating the United States, which PCT application is in turn a continuation-in-part of U.S. application Ser. No. 08/257593, filed Jun. 9, 1994, U.S. Pat. No. 5,631,365, which is a continuation-in-part of U.S. application Ser. No. 08/102,440, filed Sep. 21, 1993, abandoned.

BACKGROUND OF THE INVENTION

The present invention relates to hydroxy-substituted azetidinones useful as hypocholesterolemic agents in the treatment prevention of atherosclerosis, and to the combination of a hydroxy-substituted azetidinone of this invention and a cholesterol bioxynthesis inhibitor for the treatment and prevention of atherosclerosis. The invention also relates to a process for preparing hydroxy-substituted azetidinones.

Atherosclerotic coronary heart disease (CHD) represents the major cause for death and cardiovascular morbidity in the western world. Risk factors for atherosclerotic coronary heart disease include hypertension, diabetes mellitus, family history, male gender, cigar smoke and serum cholesterol. A total cholesterol level in excess of 225–250 mg/dl is associated with significant elevation of risk of CHD.

Cholesteryl esters are a major component of atherosclerotic lesions and the major storage form of cholesterol in arterial wall cells. Formation of cholesteryl esters is also a key step in the intestinal absorption of dietary cholesterol. Thus, inhibition of cholesteryl ester formation and reduction of serum cholesterol is likely to inhibit the progression of atherosclerotic lesion formation, decrease the accumulation of cholesteryl esters in the arterial wall, and block the intestinal absorption of dietary cholesterol.

A few azetidinones have been reported as being useful lowering cholesterol and/or in inhibiting the formation of cholesterol-containing lesions in mammalian arterial walls. U.S. Pat. No. 4,983,597 discloses N-sulfonyl-2-azetidinones as anticholesterolemic agents and Ram, et al., in *Indian J. Chem.*, Sect. B. 29B, 12 (1990), p. 1134–7, disclose ethyl 4-(2-oxoazetidin-4-yl)phenoxy-alkanoates as hypolipidemic agents. European Patent Publication 264,231 discloses 1-substituted-4-phenyl-3-(2-oxo-alkylidene)-2-azetidinones as blood platelet aggregation inhibitors. European Patent 199,630 and European Patent Application 337,549 disclose elastase inhibitory substituted azetidinones said to be useful treating inflammatory conditions resulting in tissue destruction which are associated with various disease states, e.g. atherosclerosis.

WO93/102048, published Feb. 4, 1993, discloses substituted β-lactams useful as hypocholesterolemic agents.

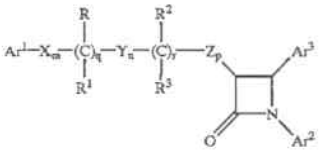
The regulation of whole-body cholesterol homeostasis in humans and animals involves the regulation of dietary cholesterol and modulation of cholesterol biosynthesis, bile acid biosynthesis and the catabolism of the cholesterol-containing plasma lipoproteinis. The liver is the major organ responsible for cholesterol biosynthesis and catabolism and for this reason, it is a prime determinant of plasma cholesterol levels. The liver is the site of synthesis and secretion of very low density lipoproteins (VLDL) which are subsequently metabolized to low density lipoproteins (LDL) in the circulation. LDL are the predominant cholesterol-carrying lipoproteins in the plasma and an increase in their concentration is correlated with increased atherosclerosis.

When intestinal cholesterol absorption is reduced, by whatever means, less cholesterol is delivered to the liver. The consequence of this action is decreased hepatic lipoprotein (VLDL), production and an increase in the hepatic clearance of plasma cholesterol, mostly as LDL. Thus, the net effect of inhibiting intestinal cholesterol absorption is a decrease in plasma cholesterol levels.

The inhibition of cholesterol biosynthesis by 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase (EC1.1.1.34) inhibitors has been shown to be an effective way to reduce plasma cholesterol (Witzum, *Circulation*, 80, 5 (1989), p. 1101–1114) and reduce atherosclerosis. Combination therapy of an HMG CoA reductase inhibitor and a bile acid sequestrant has been demonstrated to be more effective in human hyperlipidemic patients than either agent in monotherapy (Illingworth, Drugs, 36 (Suppl. 3) (1988), p. 63–71).

SUMMARY OF THE INVENTION

Novel hypocholesterolemic compounds of the present invention are represented by the formula I



I

or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 and Ar^2 are independently selected from the group consisting of aryl and R^4-substituted aryl;

Ar^3 is aryl or R^5-substituted aryl;

X, Y and Z are independently selected from the group consisting of —CH_2—, —CH(lower alkyl)— and —C(dilower alkyl)—;

R and R^2 are independently selected from the group consisting of —OR^6, —$O(CO)R^6$, —$O(CO)OR^9$ and —$O(CO)NR^6R^7$;

R^1 and R^3 are independently selected from the group consisting of hydrogen, lower alkyl and aryl;

q is 0 or 1; r is 0 or 1; m, n and p are independently 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q are r is 1, 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4, or 5;

$R^4$is 1–5 substituents independently selected from the group consisting of lower alkyl, —OR^6, —$O(CO)[R_6,]R^6$, —$O(CO)OR^9$, —$O(CH_2)_{1-5}OR^6$, —$O(CO)NR^6R^7$, —NR^6R^7, —$NR^6(CO)R^7$, —$NR^6(CO)OR^9$, —$NR^6(CO)NR^7R^8$, —$NR^6SO_2R^9$, —$COOR^6$, —$CONR^6R^7$, —COR^6, —$SO_2NR^6R^7$, $S(O)_{0-2}R^9$, —$O(CH_2)_{1-10}$—$COOR^6$, —$O(CH_2)_{1-10}CONR^6R^7$, —(lower alkylene)$COOR^6$, —CH═CH—$COOR^6$, —CF_3, —CN, —NO_2 and halogen;

R^5 is 1–5 substituents independently selected from the group consisting of —OR^6, —$O(CO)R^6$, —$O(CO)OR^9$, —$O(CH_2)_{1-5}OR^6$, —$O(CO)NR^6R^7$, —NR^6R^7, —$NR^6(CO)R^7$, —$NR^6(CO)OR^9$, —$NR^6(CO)NR^7R^8$, —$NR^6SO_2R^9$, —$COOR^6$, —$CONR^6R^7$, —COR^6, —$SO_2NR^6R^7$, $S(O)_{0-2}R^9$, —$O(CH_2)_{1-10}$—$COOR^6$, —$O(CH_2)_{1-10}CONR^6R^7$, —(lower alkylene)$COOR^6$ and —CH═CH—$COOR^6$;

R^6, R^7 and R^8 are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

R^9 is lower alkyl, aryl or aryl-substituted lower alkyl.

R^4 is preferably 1–3 independently selected substituents, and R^5 is preferably 1–3 independently selected substituents. Preferred are compounds of formula I wherein Ar^1 is phenyl or R^4-substituted phenyl, especially (4-R^4)-substituted phenyl, Ar^2 is preferably phenyl or R^4-substituted phenyl, especially (4-R^4)-substituted phenyl. Ar^3 is preferably R^5-substituted phenyl, especially (4-R^5)-substituted phenyl. When Ar^1 is (4-R^4)-substituted phenyl, R^4 is preferably a halogen. When Ar^2 and Ar^3 are R^4- and R^5-substituted phenyl, respectively, R^4 is preferably halogen or —OR^6 and R^5 is preferably —OR^6, wherein R_6 is lower alkyl or hydrogen. Especially preferred are compounds wherein each of Ar^1 and Ar^2 is 4-fluorophenyl and Ar^3 is 4-hydroxyphenyl or 4-methoxyphenyl.

X, Y and Z are each preferably —CH_2—. R^1 and R^3 are each preferably hydrogen. R and R^2 are preferably —OR^6 wherein R^6 is hydrogen, or a group readily metabolizable to a hydroxyl (such as —O(CO)R^6, [—O(CO)OR^9 and] —OR^6, especially —O(CO)NR^8R^7, defined above).

The sum of m, n, p, q and r is preferably 2, 3 or 4, more preferably 3. Preferred are compounds wherein m, n and r are each zero, q is 1 and p is 2. Also preferred are compounds wherein p, q and n are each zero, r is 1 and m is 2 or 3. More preferred are compounds wherein m, n and r are each zero, q is 1, p is 2, Z is —CH_2 and R is —OR^6OR_6, especially when R^6 is hydrogen. Also more preferred are compounds wherein p, q and n are each zero, r is 1, m is 2, X is —CH_2— and R^2 is —OR^6, especially when R^6 is hydrogen.

Another group of preferred compounds is that wherein Ar^1 is phenyl or R^4-substituted phenyl, Ar^2 is phenyl or R^4-substituted phenyl and Ar^3 is R^5-substituted phenyl. Also preferred are compounds wherein Ar^1 is phenyl or R^4-substituted phenyl, Ar^2 is phenyl or R^4-substituted phenyl, Ar^3 is R^5-substituted phenyl, and the sum of m, n, p, q and r is 2, 3 or 4, more especially 3. More preferred are compounds wherein Ar^1 is phenyl or R^4-substituted phenyl, Ar^2 is phenyl or R^4-substituted phenyl Ar^3 is R^5-substituted phenyl, and wherein m, n and r are each zero, q is 1 and p is 2, or wherein p, q and n are each zero, r is 1 and m is 2 or 3.

This invention also relates to a method of lowering the serum cholesterol level in a mammal in need of such treatment comprising administering an effective amount of a compound of formula I. That is, the use of a compound of the present invention as an hypocholesterolemic agent is also claimed.

In still another aspect, the present invention relates to a pharmaceutical composition comprising a serum cholesterol-lowering effective amount of a compound of formula I in a pharmaceutically acceptable carrier.

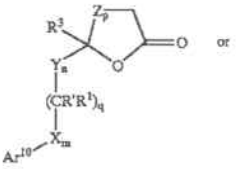
The present invention also relates to a method of reducing plasma cholesterol levels, and to a method of treating or preventing atherosclerosis, comprising administering to a mammal in need of such treatment an effective amount of a combination of a hydroxy-substituted azetidinone cholesterol absorption inhibitor of formula I and a cholesterol biosynthesis inhibitor. That is, the present invention relates to the use of a hydroxy-substituted azetidinone cholesterol absorption inhibitor of formula I for combined use with a cholesterol biosynthesis inhibitor (and, similarly, use of a cholesterol biosynthesis inhibitor for combined use with a hydroxy-substituted azetidinone cholesterol absorption inhibitor of formula I) to treat or prevent atherosclerosis or to reduce plasma cholesterol levels.

In yet another aspect, the invention relates to a pharmaceutical composition comprising an effective amount of a hydroxy-substituted azetidinone cholesterol absorption inhibitor of formula I, a cholesterol biosynthesis inhibitor, and a pharmaceutically acceptable carrier. In a final aspect, the invention relates to a kit comprising in one container an effective amount of a hydroxy-substituted azetidinone cholesterol absorption inhibitor of formula I in a pharmaceutically acceptable carrier, and in a separate container, an effective amount of a cholesterol biosynthesis inhibitor in a pharmaceutically acceptable carrier.

In yet another aspect, the invention relates to a process for preparing certain compounds of formula I comprising the steps:

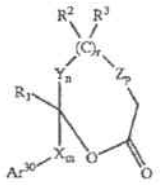
(a) treating with a strong base a lactone of the formula

A



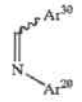
or

B



wherein R' and $R^{2'}$ are R and R^2, respectively, or are suitably protected hydroxy groups; Ar^{10} is Ar^1, a suitably protected hydroxy substituted aryl or a suitably protected amino-substituted aryl; and the remaining variables are as defined above, provided that in lactone of formula B when n and r are each zero, p is 1–4;

(b) reacting the product of step (a) with an imine of the formula



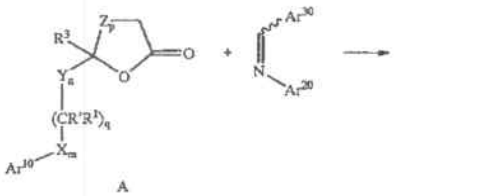
wherein Ar^{20} is Ar^2, a suitably protected hydroxy-substituted aryl or a suitably protected amino-substituted aryl; and Ar^{30} is Ar^3, a suitably protected hydroxy-substituted aryl or a suitably protected amino-substituted aryl;

c) quenching the reaction with an acid;

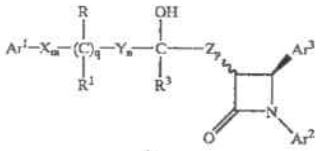
d) optionally removing the protecting groups from R', $R^{2'}$, Ar^{10}, Ar^{20} and Ar^{30}, when present; and

e) optionally functionalizing hydroxy or amino substituents at R, R^2, Ar^1, Ar^2 and Ar^3.

Using the lactones shown above, compounds of formula IA and IB are obtained as follows:

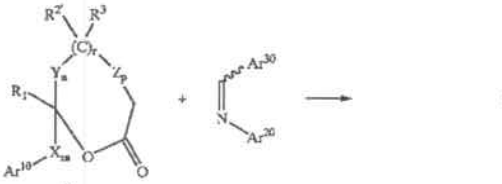


A

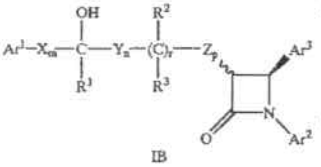


IA

wherein the variables are as defined above; and



B



IB

wherein the variables are as defined above.

DETAILED DESCRIPTION

As used herein, the term "lower alkyl" means straight or branched alkyl chains of 1 to 6 carbon atoms.

"Aryl" means phenyl, naphthyl, indenyl, tetrahydronaphthyl or indanyl.

"Halogen" refers to fluorine, chlorine, bromine or iodine atoms.

The above statement, wherein R^6, R^7 and R^8 are said to be independently selected from a group of substituents, means that R^6, R^7 and R^8 are independently selected, but also that where an [R_6], R^6 or R^8 variable occurs more than once in a molecule, those occurrences are independently selected (e.g., if R is —OR^5 wherein R^6 is hydrogen, R^4 can be —OR^5 wherein R^6 is lower alkyl).

Compounds of the invention have at least one asymmetric carbon atom and therefore all isomers, including enantiomers and diastereomers are contemplated as being part of this invention. The invention includes d and [l] *l* isomers in both pure form and in admixture including racemic mixtures. Isomers can be prepared using conventional techniques, either by reacting chiral starting materials or by separating isomers of a compound of formula I. Isomers may also include geometric isomers, e.g. when a double bond is present. All such geometric isomers are contemplated for this invention.

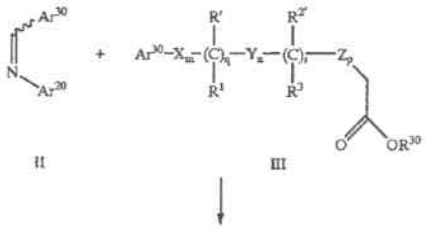
Those skilled in the art will appreciate that for some compounds of formula I, one isomer will show greater pharmacological activity than another isomer.

Compounds of the invention with an amino group can form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salt is prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt. The free base form may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium bicarbonate. The free base form differs from its respective salt form somewhat in certain physical properties, such as solubility in polar solvents, but the salt is otherwise equivalent to its respective free base form for purposes of the invention.

Certain compounds of the invention are acidic (e.g., those compounds which possess a carboxyl group). These compounds form pharmaceutically acceptable salts with inorganic and organic bases. Examples of such salts are the sodium, potassium, calcium, aluminum, gold and silver salts. Also included are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

Cholesterol biosynthesis inhibitors for use in the combination of the present invention include HMG CoA reductase inhibitors such as lovastatin, pravastatin, fluvastatin, simvastatin, and Cl-981; HMG CoA synthetase inhibitors, for example L-659,699 ((E,E)-11-[3'-R-(hydroxy-methyl)-4'-oxo-2'-R-oxetanyl]-3,5,7R-trimethyl-2,4-undecadienoic acid); squalene synthesis inhibitors, for example squalestatin 1; and squalene epoxidase inhibitors, for example, NB-598 ((E)-N-ethyl-N-(6,6-dimethyl-2-hepten-4-ynyl)-3-[(3,3'-bithiophen-5-yl)methoxy]benzene-methanamine hydrochloride) and other cholesterol biosynthesis inhibitors such as DMP-565. Preferred HMG CoA reductase inhibitors are lovastatin, pravastatin and simvastatin.

Compounds of formula I can be prepared by known methods, for example those described below and in WO93/02048.



II III

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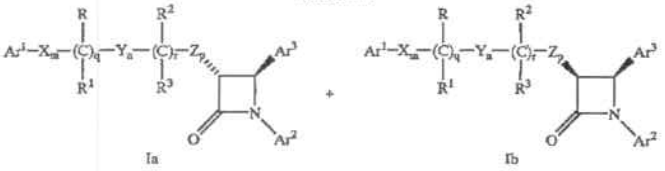


Ia Ib

Compounds of formula Ia and Ib, wherein Ar^1, Ar^2, [Ar3,] Ar^3 X, Y, Z, R^1, R^2, R^3, m, n, p, q and r are as defined above, can be prepared by treatment of an ester of formula III, wherein R^{10} is lower alkyl such as ethyl or a chiral moiety such as menthyl or 10-(diisopropylsulfonamido)isobornyl, and the remaining variables are as defined above, with a strong base such as lithium diisopropylamide (LDA) in a suitable solvent such as tetrahydrolithium (THF) at −78° C. A solubilizing agent such as hexamethylphosphoric triamide (HMPA) may optionally be added as a cosolvent. An imine of formula II, wherein Ar^{20} and Ar^{30} are as defined above, is added, the reaction mixture is either warmed to room temperature or maintained at a suitable low temperature such as −78° C. for the appropriate time, followed by quenching with a suitable acid such as 1N HCl. The product is isolated using conventional purification techniques. When a protecting group as defined in Table 1 (below) is present on one or more of the optionally protected groups, an additional step comprising removal of the protecting group by conventional techniques is needed. However, for compounds of formula Ia, Ib, or any compound of formula I wherein a protected hydroxy group Ar^{10}, Ar^{20}, Ar^{30}, R' or $R^{2'}$ is an alkoxy or benzyloxy group, such a protecting group need not be removed to obtain a compound of formula I. When a chiral ester of formula III is used, the resulting compound of formula Ia or Ib is not racemic.

Imines of formula II (Ar^{30}—CH═N—Ar^{20}) can be prepared from aldehydes of the formula Ar^{30}—CHO and amines of the formula [Ar^+—CHO and] Ar^{20}—NH_2 by procedures well known in the art. Aldehydes of formula [Ar^+] Ar^{30}—CHO and amines of formula Ar^{20}—NH_2 are commercially available or can be prepared via known procedures.

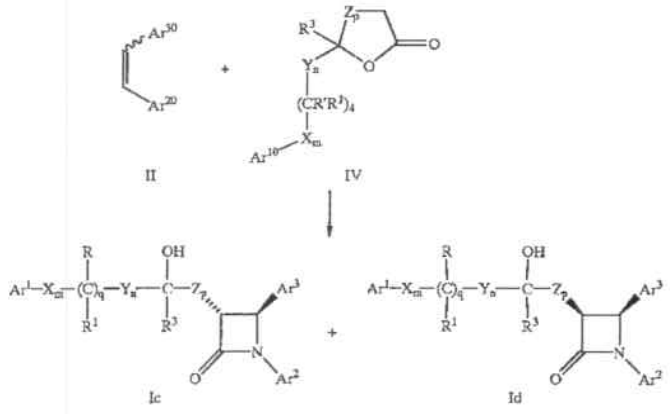
Compounds of formula Ic and Id, wherein the variables are as defined above, can be prepared by a process comprising the following steps:

(a) Treat a lactone of formula IV, wherein the variables are as defined above, with a strong base such as an alkyllithium (e.g., n-butyl-lithium), a metal hydride (e.g., sodium hydride), a metal alkoxide (e.g., sodium methoxide), a metal halide (e.g., $TiCl_4$), metal exchange of the lithium enolate with a metal halide (e.g., zinc chloride), metal exchange of the lithium enolate with a metal alkyl (e.g., 9-borabicyclononyl triflate), or, preferably, a metalamide (e.g., LDA), in a suitable anhydrous organic solvent such as dry THF, ether or benzene, in a dry, inert atmosphere, e.g., under nitrogen. The reaction is carried out at about 0° C. to about −85° C., preferably about −78° C., over a period of about 5 to about 60 minutes, preferably about 30 minutes. 1–50% of solubilizing cosolvents may optionally be added, preferably about 10% HMPA.

(b) Add an imine of formula II, wherein Ar^{20} and Ar^{30} are as defined above, to the product of step (a) over a period of 5 to 60 minutes, preferably 30 minutes, maintaining the reaction mixture at about 0° C. to about −85° C., preferably about −78° C., for 1 to 12 hours, preferably about 3 hours, or warming the reaction mixture over that time period at a rate of about 10° C. per hour to about 70° C. per hour, preferably about 30° C. per hour, to a temperature of about 20° C.

(c) Quench the reaction with a suitable acid such as HCl (1N).

(d) The protecting groups on R', $R^{2'}$, Ar^{10}, Ar^{20} and Ar^{30}, when present, are removed, if desired, by methods well known in the art, for example silyl protecting groups are removed by treatment with fluoride.



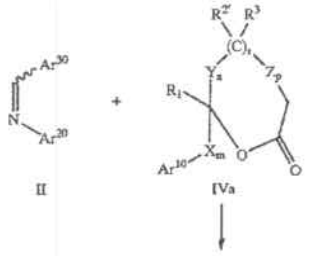
II IV

Ic Id

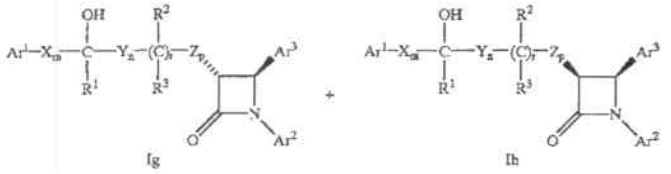
e) Compounds of formula I wherein any of R and R^2, when present, are OR^6 wherein R^6 is hydrogen, can be converted by well known methods to other compounds of formula I wherein R and R^2 are functionalized, i.e., are independently selected from the group consisting of OR^{6a}, —O(CO)R^5, —O(CO)OR^5 and —O(CO)NR^6R^7, wherein R^5, R^7 and R^9 are as defined above and R^{6a} is lower alkyl, aryl, or aryl-lower alkyl. For example, treatment of the alcohol with an alkyl halide in the presence of a suitable base such as NaH will afford alkoxy-substituted compounds (i.e., R or R^2 is OR^6, wherein R^6 is lower alkyl); treatment of the alcohol with an acylating agent such as acetylchloride will result in compounds wherein R or R^2 is —OC(O)R^6; treatment of the alcohol with phosgene followed *by an* alcohol of the formula HOR^9 affords compounds substituted with a —OC (O)OR^9 group; and treatment of the alcohol with phosgene followed by an amine of the formula HNR^6R^7 affords compounds wherein R or R^2 is —OC(O)NR^6R^7. Compounds of formula I wherein any Ar^1, Ar^2 or Ar^3 has a hydroxy or amino group can be similarly functionalized to obtain other compounds of formula 1, i.e., wherein R^4 and R^5 are independently $—OR^{6a}$, —O(CO)R^6, —O(CO)OR^9, —O$(CH_2)_{1-5}OR^5$, —O(CO)NR^6R^7, —NR^6R^7, —NR^5(CO)R^7, —NR^6(CO)OR^9, —NR^5(CO)NR^7R^8 or —$NR^6SO_2R^9$.

The product of step c, d or e is isolated using conventional purification techniques such as extraction, crystallization or, preferably, silica gel 60 chromatography. When a chiral lactone is used, the resulting compound of formula Ic or Id is not racemic.

Using the procedure described in steps (a)–(e), lactones of formula IVa can be used to prepare compounds of formula Ig and Ih, provided that when n and r are each zero, p is 1–4:



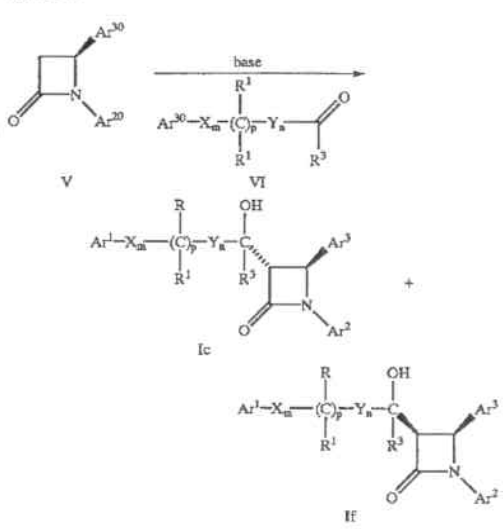
II IVa



Ig Ih

Lactones of formulae IV and IVa are known in the art or can be prepared by methods well known in the art. See, for example, U.S. Pat. No. 4,375,475 and *J. Agric. Food Chem.*, 30 (5) (1982) p. 920-4.

Method B:

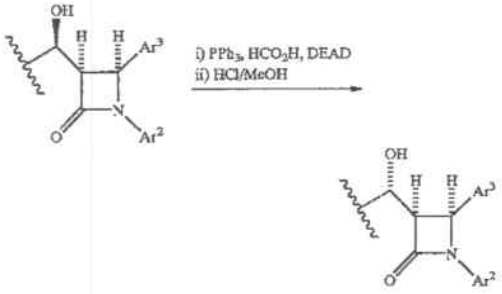


V VI Ic If

Azetidinones of formula V, wherein Ar^{20} and Ar^{30} are as defined above, can be reacted to form compounds of formula Ie and If i.e., compounds of formula I wherein r is 1, R^2 is hydroxy, and p is zero) by treatment of azetidinone V with a strong base such as lithium [iosopropylcyclohexylamide] *isopropylcyclohexylamide* in a suitable solvent such as THF in the presence or [absent] *absence* of HMPA at −78° C., followed by the addition of an aldehyde or ketone of VI, wherein Ar^{10}, X, Y, R', R^2, R^3, m, n and q are as defined

above. As in the case of Method A, protecting groups at Ar^{10}, Ar^{20}, Ar^{30}, R' and R$^{2'}$ are removed as necessary.

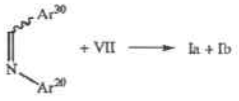
This process provides several of the possible diastereomers which can be separated by a combination of crystallization, silica gel chromatography and HPLC, using techniques well known in the art. The remaining diastereomers can be obtained by inversion reactions such as the Mitsunobu reaction sequence outlined below, wherein partial structures of formula If are shown:

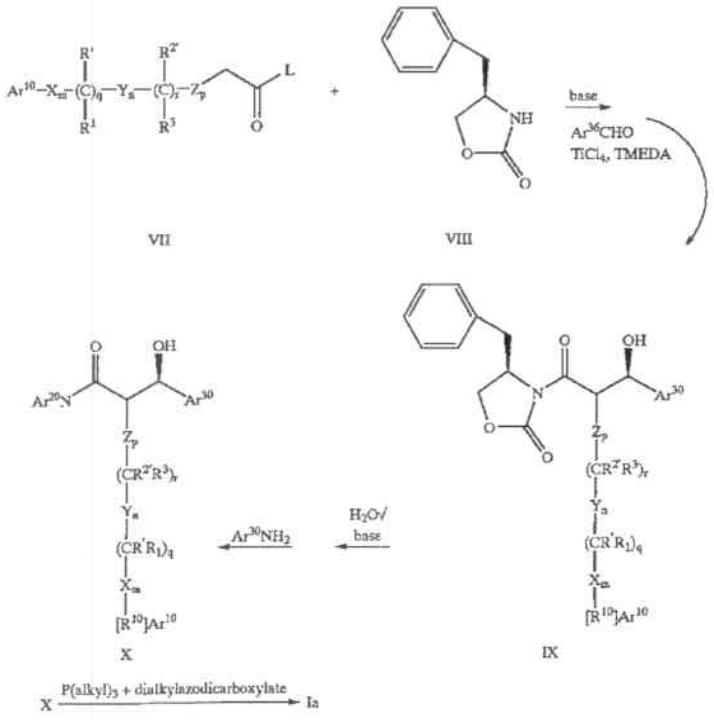


In the above known process, DEAD is diethylazodicarboxylate and PPh_3 is triphenylphosphine. The reactants are stirred at room temperature overnight and the resultant formate ester is converted to the corresponding hydroxy compound with the desired stereochemistry.

Compounds of formula Ia as defined above can be prepared by reacting a chiral auxiliary such as the compound of formula VIII with an activated carboxylic acid derivative of formula VII, for example an acid chloride (L═Cl), a mixed anhydride formed with phenyl phosphorodichloridate (L═OP(O)(Cl)OPh), an N-methyl-pyridinium ester formed from the reaction of an acid with N-methyl-2-chloropyridinium iodide (L═2-oxy-N-methylpyridinium iodide), and a 2-thiopyridyl ester formed from the reaction of an acid chloride and 2-thiopyridine, wherein the remaining variables are as defined above; enolizing the resultant product, for example with $TiCl_4$ and tetramethylethylenediamine (TMEDA); condensing with an aldehyde, $Ar^{30}CHO$; hydrolyzing to the corresponding acid, then reacting the compound of formula IX with an amine, $Ar^{20}NH_2$; and cyclizing the resultant compound of formula X, with, for example a trialkylphosphine and a dialkylazodicarbo)ylate. As in the case of Method A, protecting groups at Ar^{10}, Ar^{20}, Ar^{30}, R' and R$^{2'}$ are removed as necessary. This procedure is described in detail in [WO93/102048] *WO93/02048*.

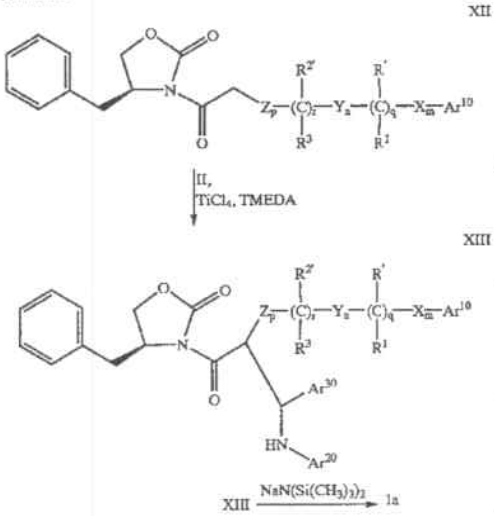
II





Compounds of formula Ia as defined above can also be prepared treatment of an imine of formula [11,] *II*, wherein Ar^{20} and Ar^{30} are as defined above, with an activated carboxylic acid derivative of formula VII as defined above in the presence of a tertiary amine base such as triethylamine, tributylamine or diethylisopropylamine in an inert solvent such as CH_2Cl_2. Again, as in the case of Method A, protecting groups at Ar^{10}, Ar^{20}, Ar^{30}, R' and $R^{2'}$ are removed as necessary. Use of other bases, e.g., pyridine, favors formation of compounds of formula Ib.

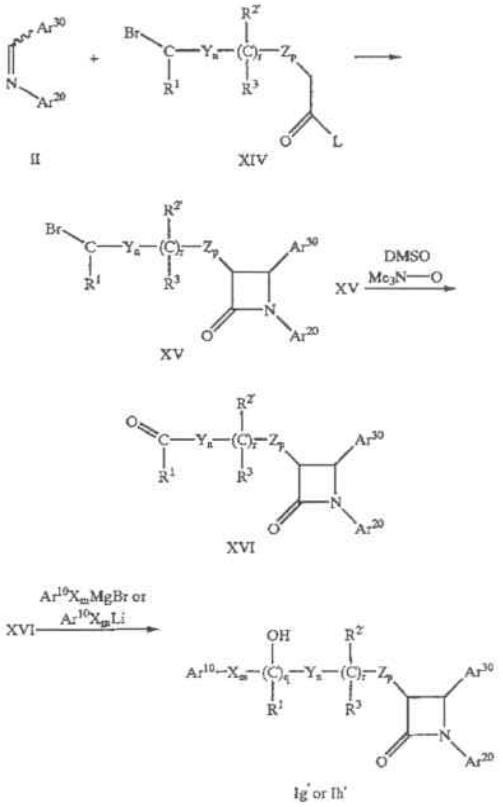
Method E:



In the first step, compound XII is dissolved in a suitable solvent, e.g., anhydrous CH_2Cl_2, and treated with a Lewis acid, e.g., $TiCl_4$ at about −60° C. to 0° C., preferably at about −25° C., under a dry, inert atmosphere, e.g., argon. A tertiary amine base such as TMEDA is added and the mixture stirred at about −60° C. to 0° C., preferably at about −25° C. to −15° C., for a period of about 1 h. An imine of formula $Ar^{30}CH{=}NAr^{20}$ is added neat or optionally as a solution in a suitable solvent, e.g. anhydrous CH_2Cl_2, over a period of about 5 min, and the reaction is stirred vigorously at about −60° C. to 0° C., preferably at about −25° C. to −15° C., for about 3 to 6 h, preferably about 4 h or until the reaction is complete by TLC. An acid, e.g. acetic acid, is added to reaction at the reaction temperature and the mixture is allowed to warm to room temperature slowly with stirring for about 1–3 hours, preferably about 2 hours. The compound of formula XII is isolated by extraction with a suitable solvent, e.g. CH_2Cl_2, then purified by crystallization or silica gel chromatography.

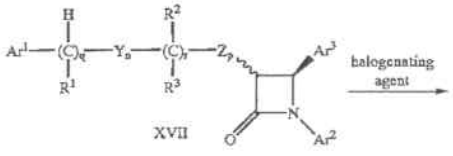
In the second step, the product is treated with a strong non-nucleophilic base, such as sodium or lithium bistrimethylsilylamide at about −78° C. to 100° C. After reaction, the mixture is poured into aqueous tartaric acid and the product isolated from the organic layer. As in the case of Method A, protecting groups at Ar^{10}, Ar^{20}, Ar^{30}, R' and $R^{2'}$ are removed as necessary. This process, including the preparation of the starting material of formula XII, is also described in greater detail in WO93/02048.

Method F:



Compound of formula Ig' and Ih' (i.e., compounds of formula I wherein R is OH), wherein $R^{2'}$ is a protected hydroxy group as defined above, and the remaining variables are as defined above, can be prepared by reacting an imine of formula [11] *II* and a carboxylic acid derivative of formula XIV, wherein the variables are as defined above, according to Method D, followed by oxidation of the resultant halide of formula XV by treatment with an oxidizing agent such as trimethylamine oxide, CrO_3 or ozone in a solvent such as DMSO. The resultant aldehyde or ketone of formula XVI is then reacted with an aryl organometallic reagent (e.g., $Ar^{10}X_mMgBr$, $Ar^{10}X_mLi$, $Ar^{10}X_mMgCl$ or $Ar^{10}X_mCeCl_2$) to obtain a compound of formula Ig' or Ih'. As described above, the Ar^{10}, Ar^{20}, Ar^{30} and $R^{2'}$ substituents can be converted to the desired Ar^1, Ar^2, Ar^3 and R^2 substituents by procedures well known in the art.

Method G:



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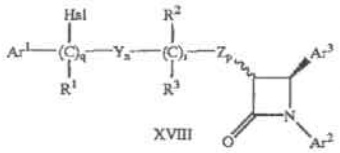
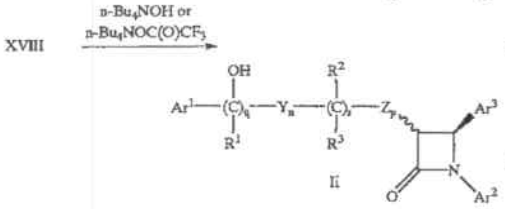
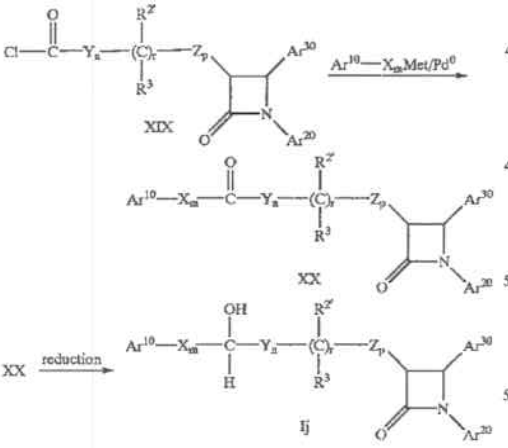


XVIII



Compounds of formula Ii having a hydroxy substituent on the side chain adjacent to the Ar^1 group (i.e., compounds of formula I wherein m is 0) can be prepared by heating a compound of formula XVII, prepared by Method D, above, wherein the variables are as defined above, for about 1–6 hours at about 60° C. to 100° C. with a halogenating agent such as N-bromosuccinimide (NBS) in a suitable solvent such as CCl_4 in the presence of an initiating agent such as benzoyl peroxide. The resultant compound of formula XVIII, wherein Hal is Cl, Br or I and the remaining variables are as defined above, is then heated in a suitable solvent such as CH_2Cl_2 with a tetraalkyl-ammonium salt such as tetra n-butyl-ammonium hydroxide (n-Bu_4NOH) to obtain the compound of formula Ia. Alternatively, compound XVIII can be heated in a suitable solvent such as CH_2Cl_2 with tetra n-butylammonium trifluoroacetate (n-$Bu_4NOC(O)CF_3$) followed by treatment with a mild base such as ethanol saturated with [NH3] NH_3 to obtain compound Ii,

Method H:

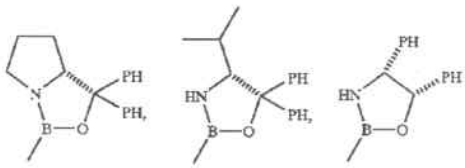


Compounds of formula Ij (i.e., compounds of formula I wherein R is OH, R^1 is H and q is 1) are prepared from compound XIX in 2 steps. First, a compound of formula XIX, wherein the variables are as defined above, is dissolved in a suitable anhydrous solvent, e.g. THF, at about –20° C. to about 22° C., preferably at about 0° C. under a dry inert atmosphere, e.g. argon and adding a transition metal source, e.g. tetrakis(triphenylphosphine)-palladium or palladium acetate/triphenyl phosphine. An organometallic of formula

Ar^{10}-X[m]$_m$-Met, wherein in Ar^{10}, X and m are as defined above and Met is, for example, ZnCl or $B(OH)_2$, is added to the reaction mixture at about –20° C. to about 22° C., preferably at about 0° C., the reaction mixture is stirred for about 15 min to 4 h, preferably about 1 h, and is then allowed to warm to about 22° C. Addition of dilute acid, e.g. 1N HCl, followed by extraction with a suitable organic solvent, e.g. ethyl acetate (EtOAc), produces compound XX.

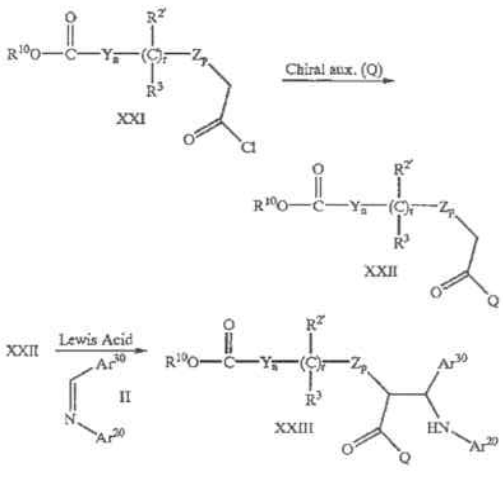
The ketone of-formula XX is dissolved in a suitable *solvent* e.g. CH_3OH, a hydrogenation catalyst is added, e.g. Pd on carbon, and the mixture is exposed to H_2 gas under a pressure of about 14 psi to 100 psi, preferably about 60 psi for about 1 to 24 h, preferably, about 16 h. The hydrogenation catalyst is removed by filtration and the solvent is removed in vacuo to produce a compound Ij as a mixture of alcohol diastereomers which can be separated by conventional means.

Alternatively, a ketone of formula XX is dissolved in a suitable solvent, e.g. THF, at about –40° C. to about 22° C., preferably at about 0° C., and a suitable reducing agent such as $NaBH_4$, a substituted borohydride (e.g., [cbz-proline]$_3$BHNa) or a borane is added, optionally in the presence of a suitable chiral promotor present either in catalytic or stoichiometric amounts, e.g., chiral borane of structures:



Addition of dilute acid, e.g., 1N HCl, followed by extraction with a suitable solvent produces compounds of formula Ij. As above, protecting groups at Ar^{10}, Ar^{20}, Ar^{30} and $R^{2'}$ are removed as necessary. When either a chiral reagent or a chiral promotor is used, the resulting product is non-racemic.

Compounds of formula XIX can be prepared by a multi-step procedure as represented below:



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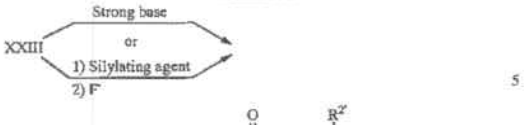
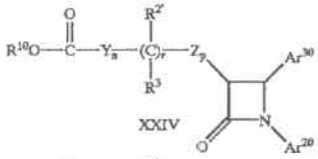
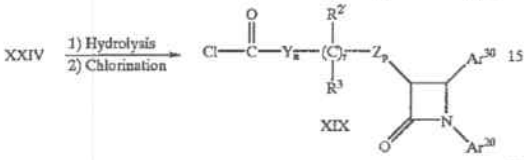




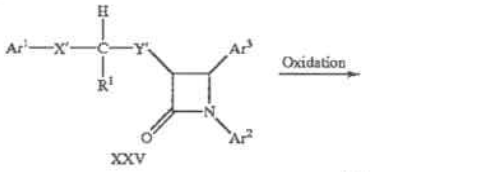


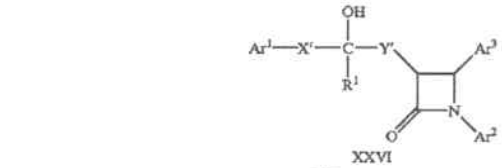
Compounds of formula XXI, wherein R^{10} is lower alkyl and the remaining *variables are as defined above, are commercially available or can be prepared by treating the corresponding carboxylic acid (i.e., compounds wherein the Cl is replaced by a hydroxy group) with a chlorinating agent, e.g. $SOCl_2$ or oxalyl chloride, under a dry atmosphere, neat or in a suitable inert organic solvent, e.g. toluene at about 40° C. to 110° C., preferably about 70° C.; alternatively, a catalyst made be added, e.g. dimethylformamide (DMF), the reaction is conducted at about 22° C., and the solvent and excess reagents are removed in vacuo. The compound XXI is reacted with a chiral auxiliary such as (S)-4-phenyl-2-oxazolidinone according to the following procedure; a chiral auxiliary is treated with a strong base such as an alkyllithium, a metal hydride or a tertiary amine base such as triethylamine, in a suitable anhydrous organic solvent, e.g., dry THF, under a dry, inert atmosphere, e.g. argon at about –85° C., to 22° C., preferably about 0° C., for about 10 min to 60 min, preferably about 30 minutes. The resulting anion is reacted, without isolation, with compound XXI in a suitable anhydrous organic solvent, e.g. dry THF, under a dry, inert atmosphere, e.g. argon at about –85° C. to about 22° C., preferably 0° C., for about 30 min to 60 min, preferably 30 min. The reaction is warmed to about 22° C. and continued for 1 to 12 h, preferably 6 h. Water is added and compound XXII is isolated by extraction and purified by crystallization.*

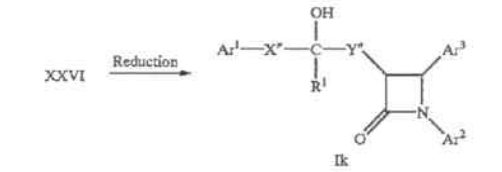
The compound of formula XXII is treated in the same manner as described in step 1 of Method E to obtain a compound XXIII.

Azetidinone ring closure can be accomplished by alternative procedures. By one method, a compound of formula XXIII is treated with a strong non-nucleophilic base, such as sodium or lithium-bistrimethylsilylamide, in a suitable inert organic solvent, e.g. CH_2Cl_2, at about –78° C. to about 10° C., preferably about 0° C. The mixture is stirred for about 1 to 2 hours while gradually warming to about 22° C. Compound XXIV is isolated by conventional extraction with CH_2Cl_2. In another, two-step method, a compound of formula XXIII is first treated with mild silylating agent, e.g. N,O-bis(trimethylsilyl)acetamide at about 0° C. to about 100° C., preferably about 40° C. for about 10 min to 60 min, preferably 30 min, then treated with a fluoride anion source, e.g. tetrabutylammonium fluoride (TBAF), at about 0° C. to about 100° C., preferably 40° C., and allowed to stir for about 0.5 to about 4 hours, preferably about 2 hours. Compound XXIV is isolated by conventional extraction methods.

The compound of formula XXIV is hydrolysed by a suitable base, e.g. LiOH, in a suitable solvent, e.g. 66% CH_3OH/water at about 0° C. to about 50° C., preferably 22° C., for about 1 to 4 hours, preferably 2 hours, then extracted with a suitable solvent, e.g. EtOAc. The resulting acid is converted to the acid chloride as described above by treatment with a chlorination agent, e.g. oxalyl chloride, to afford compound



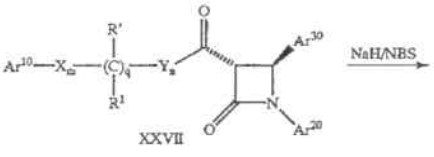




Compounds of formula Ik, wherein Ar^1, Ar^2, Ar^3 and R^1 are as defined above, one of X" and Y" is —CH_2CH_2— and the other is selected from the group consisting of —CH_2CH_2—, —CH_2—, —CH(lower alkyl)-, —CH(dilower alkyl) and a bond, are prepared by oxidation of an alkene of formula XXV, wherein one of X' and Y' is —CH=CH— and the other is —CH=CH—, —CH_2—, —CH_2CH_2—, —CH(lower alkyl)-, —CH(dilower alkyl) or a bond, and the remaining variables are as defined above, can be prepared by the following two step procedure.

A compound of formula XXV, which can be prepared by Method D, above, is treated with an oxidizing agent such as SeO_2, phenylselenic anhydride or CrO_3 in a suitable solvent such as dioxane at about 22° to 100° C. for about 0.5 to 12 hours. After the starting material is consumed as determined by TLC, or 12 hours, the reaction is cooled to about 22° C. and the product XXVI is isolated by extraction.

In the second step, an allylic alcohol of formula XXVI is dissolved in a suitable solvent, e.g., EtOAc, a hydrogenation catalyst added, e.g., Pd on carbon, and the mixture is exposed to H_2 gas under a pressure of about 14 psi to 60 psi for about 1 to 12 hours. The hydrogenation catalyst is removed in vacuo to obtain a compound of formula Ik.



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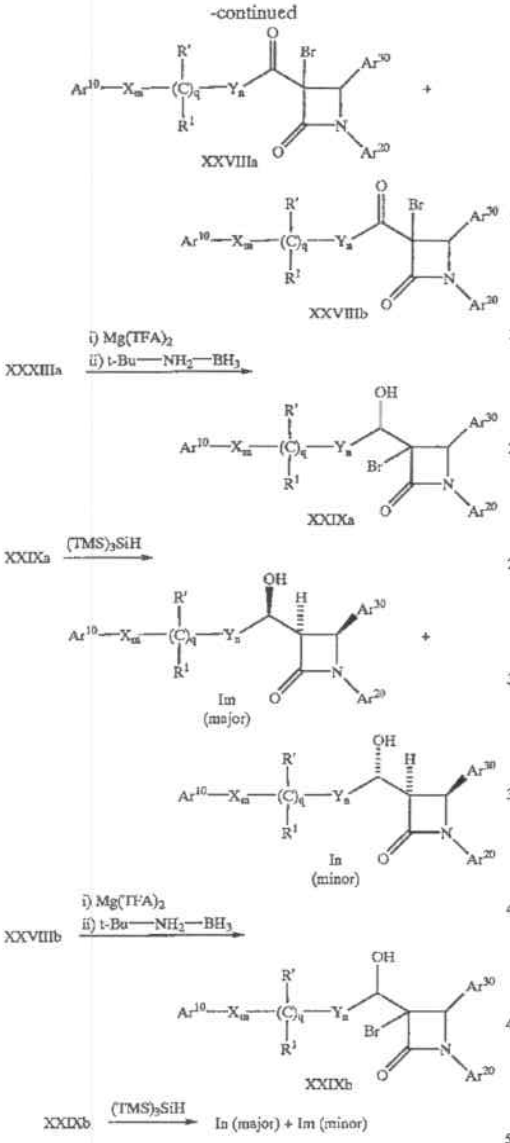


Alcohols of formula Im and In (i.e., compounds of formula I where r is 1, R^2 is —OH, R^3 is hydrogen and p is 0) can be selectively obtained from ketones of formula XXVII in three steps comprising bromination, reduction and debromination. Since the stereochemistry of the major isomers of alcohols XXIXa and XXIXb are different, one can selectively prepare either diastereomeric alcohol.

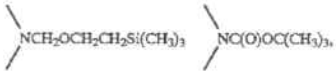
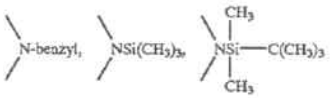
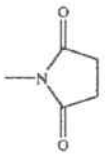
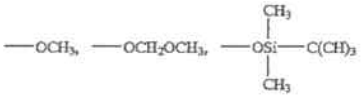
In the above process, a ketone of formula XXVII, which can be prepared by oxidation of the corresponding hydroxy compound by well known methods, is halogenated, for example by treatment in an inert solvent, e.g., THF, with NaH followed by N-bromosuccinimide, to obtain a mixture of 3-bromo-ketone compounds XXVIII (a and b). Compounds [15] XXVIIIa and XXVIIIb are then separately reduced to the corresponding alcohols, for example by treatment with magnesium trifluoroacetate ($Mg(TFA)_2$) and t-butylamine borane (t-Bu—NH_2—BH_3) in an inert solvent

such as THF at a temperature of about −78° C. to 0° C. The resultant alcohols XXIX are dehalogenated by treatment with tris(trimethylsilyl)silane ($(TMS)_3SiH$) in a solvent such as toluene in the presence of a radical initiator such as 2,2'-azobisisobutyronitrile (AIBN) to obtain a mixture of isomers Im and In which can be separated into individual enantiomers by conventional means, e.g., HPLC. Again, protecting groups at Ar^{10}, Ar^{20}, Ar^{30} and R' are removed as necessary.

Starting compounds III, V, VI, VII, VIII, XIV, XVII, XXI and XXV are all either commercially available or well known in the art and can be prepared via known methods.

Reactive groups not involved in the above processes can be protected during the reactions with conventional protecting groups which can be removed by standard procedures after the reaction. The following Table 1 shows some typical protecting groups:

TABLE 1

Group to be Protected	Group to be Protected and Protecting Group
—COOH	—COOalkyl, —COObenzyl, —COOphenyl
	
	
	
—NH_2	
—OH	
	—$OSi(CH_3)_3$, or —OCH_2phenyl

We have found that the compounds of this invention lower serum lipid levels, in particular serum cholesterol levels. Compounds of this invention have been found to inhibit the intestinal absorption of cholesterol and to significantly reduce the formation of liver cholesteryl esters in animal models. Thus, compounds of this invention are hypocholesterolemic agents by virtue of their ability to inhibit the intestinal absorption and/or esterification of cholesterol; they are, therefore, useful in the treatment and prevention of atherosclerosis in mammals, in particular in humans.

The in vivo activity of the compounds of formula I can be determined by the following procedure:

In Vivo Assay of [Hypoligidemic] *Hypolipidemic* Agents Using the Hyperlipidemic Hamster

Hamsters are separated into groups of six and given a controlled cholesterol diet (Purina Chow #5001 containing

0.5% cholesterol) for seven days. Diet consumption is monitored to determine dietary cholesterol exposure in the face of test compounds. The animals are dosed with the test compound once daily beginning with the initiation of diet. Dosing is by oral gavage of 0.2 mL of corn oil alone (control group) or solution (or suspension) of test compound in corn oil. All animals moribund or in poor physical condition are euthanized. After seven days, the animals are anesthetized by intramuscular (IM) injection of ketamine and sacrificed by decapitation. Blood is collected into vacutainer tubes containing EDTA for plasma lipid analysis and the liver excised for tissue lipid analysis. Lipid analysis is conducted as per published procedures (Schnitzer-Polokoff, R., et al. *Comp. Biochem. Physiol.*, 99A, 4 (1991), p. 665–670) and data is reported as percent reduction of lipid versus control.

The present invention also relates to a pharmaceutical composition comprising a compound of formula I and a pharmaceutically acceptable carrier. The compounds of formula I can be administered in any conventional dosage form, preferably an oral dosage form such as a capsule, tablet, powder, cachet, suspension or solution. The formulations and pharmaceutical compositions can be prepared using conventional pharmaceutically acceptable excipients and additives and conventional techniques. Such pharmaceutically acceptable excipients and additives include non-toxic compatible fillers, binders, disintegrants, buffers, preservatives, anti-oxidants, lubricants, flavorings, thickeners, coloring agents, emulsifiers and the like.

The daily hypocholesteremic dose of a compound of formula I is about 0.1 to about 30 mg/kg of body weight per day, preferably about 0.1 to about 15 mg/kg. For an average body weight of 70 kg, the dosage level is therefore from about 5 mg to about 1000 mg of drug per day, given in a single dose of 2–4 divided doses. The exact dose, however, is determined by the attending clinician and is dependent on the potency of the compound administered, the age, weight, condition and response of the patient.

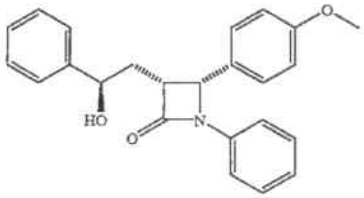
For the combinations of this invention wherein the hydroxy substituted azetidinone is administered in combination with a cholesterol biosynthesis inhibitor, the typical daily dose of the cholesterol biosynthesis inhibitor is 0.1 to 80 mg/kg of mammalian weight per day administered in single or divided dosages, usually once or twice a day; for example, for HMG CoA reductase inhibitors, about 10 to about 40 mg per dose is given 1 to 2 times a day, giving a total daily dose of about 10 to 80 mg per day, and for the other cholesterol biosynthesis inhibitors, about 1 to 1000 mg per dose is given 1 to 2 times a day, giving a total daily dose of about 1 mg to about 200 mg per day. The exact dose of any component of the combination to be administered is determined by the attending clinician and is dependent on the potency of the compound administered, the age, weight, condition and response of the patient.

Where the components of a combination are administered separately, the number of doses of each component given per day may not necessarily be the same, e.g. where one component may have a greater duration of activity, and will therefore need to be administered less frequently.

Since the present invention relates to the reduction of plasma cholesterol levels by treatment with a combination of active ingredients wherein said active ingredients may be administered separately, the invention also relates to combining separate pharmaceutical compositions in kit form. That is, a kit is contemplated wherein two separate units are combined: a cholesterol biosynthesis inhibitor pharmaceutical composition and a hydroxy substituted azetidinone cholesterol absorption inhibitor pharmaceutical composition. The kit will preferably include directions for the administration of the separate components. The kit form is particularly advantageous when the separate components must be administered in different dosage forms (e.g. oral and parenteral) or are administered at different dosage intervals.

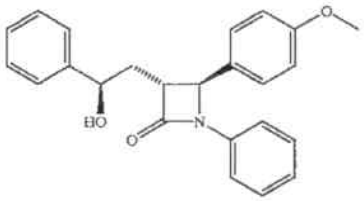
Following are examples of preparing compounds of formula I. The stereochemistry listed is relative stereochemistry unless otherwise noted. The terms cis and trans refer to the relative orientations at the azetidinone 3- and 4-positions unless otherwise indicated. The term "J" refers to the proton NMR coupling constant in hertz (Hz) between the 3- and 4-substituted protons of the azetidinone. All NMR data is of $CDCl_3$ solution unless otherwise indicated.

A



and

B

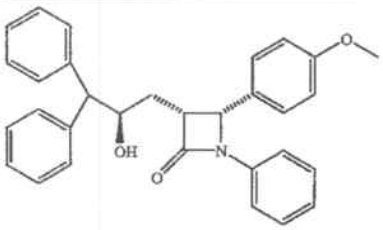


Freshly prepare a solution of lithium diisopropylamide (LDA) by dissolving diisopropylamine (1.19 g, 11.8 mmol) in anhydrous THF (20 ml) at −78° C. under argon. Add n-butyllithium (4.9 ml, 11.8 mmol, 2.4M in hexanes) and stir for 0.5 h at −78° C. To this cold solution add, 4phenylbutyrolactone (1.75 g, 10.8 mmol) in THF (4 ml) over 0.25 h, keeping the reaction temperature below −65° C. Stir at −78° C. for 0.25 h, then add 4-methoxybenzylidine anisidine (2.33 g, 11.0 mmol) in THF (8 ml) over 1 h at −78° C. Warm the reaction slowly to −50° C. over 1 h. Quench the reaction at low temperature with 1N HCl (12 ml). Partition the reaction mixture between ether and 1N HCl, wash the ether layer with water, combine the ether extracts, dry over $MgSO_4$ and concentrate in vacuo. Crystallize the crude reaction residue (3.0 g) from EtOAc-ether to obtain 1.54 g of compound A. Reconcentrate the filtrate and chromatograph on silica gel 60, eluting with 4:1 EtOAc-hexane, and isolate additional compound A (0.385 g) as well as compound B (0.420 g).

Compound A: mp 218°–220° C.; IR 1730 cm-1; CI (M–H) 374; J=5.9 Hz.

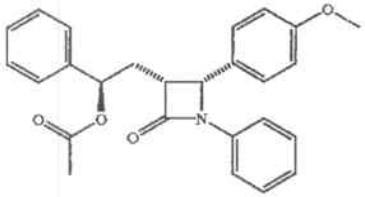
Compound B: mp 74°–76° C.; IR 1730 cm-1; CI (M+H) 374; J=2.3 Hz.

Using a similar procedure and appropriate starting materials, prepare compound 1C:



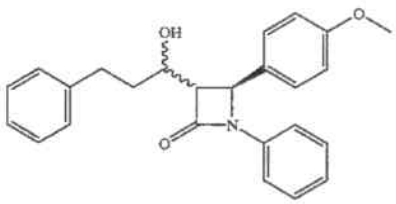
Cl(M + H) 464, J = 2.3 Hz

EXAMPLE 2



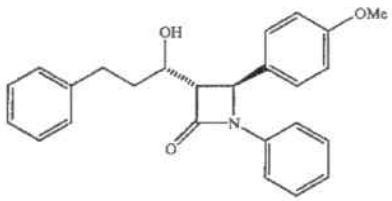
To a solution of compound A from Example 1 (0.5 g, 1.3 mmol) in anhydrous pyridine (2.7 ml), add acetic anhydride (0.63 ml, 6.7 mmol). Stir for 16 h, dilute with CH_2Cl_2 and wash 3× with 1N HCl 1× with NaCl (sat'd) and 1× with water. Concentrate the organic layer to dryness and crystallize the residue from EtOAc to obtain the title compound (0.46 g), mp 167°–169° C.; IR 1745 cm-1; EI (M+) 415; J=5.9 Hz.

EXAMPLE 3



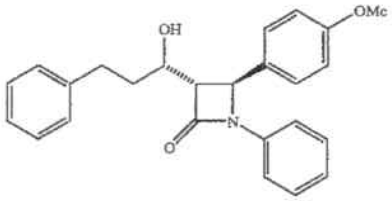
Freshly prepare a solution of lithium isopropylcyclohexylamide (LICA) by adding n-butyllithium (2.84 mL of a 1.6M solution) to 5 a solution of isopropylcyclohexylamine (0.75 mL) in THF (100 mL) at –78° C. Dissolve N-phenyl-4-(4-methoxyphenyl)-2-azetidinone (1.0 g) in THF (8 mL) and slowly add to the LICA solution at –78° C. After stirring for 20 min, add hydrocinnamaldehyde (0.54 g) and stir the reaction mixture at –78° C. for 4 h. Quench the reaction with 10% $KHSO_4$ and extract the product with EtOAc. Separate the organic layer, wash with water and NaCl (sat'd). Concentrate the extract and purify the resultant residue on a silica gel 60 column, eluting with EtOAc:hexane (15:85) to obtain 1.15 g of product as a mixture of diastereomers. Separate the diastereomers by HPLC on a silica gel column to give three diastereomers 3A, 3B and 3C:

3A



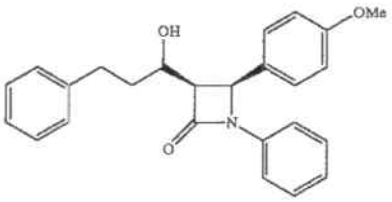
1H in $CDCl_3$:7.32–7.18(m, 11H); 7.08–6.99 (m, 1H); 6.89(d, J = 9 Hz, 2H); 4.80(d, J = 2.4 Hz, 1H); 4.10–4.00(m, 1H); 3.79(s, 3H); 3.20–3.16(m, 1H); 2.90–2.67(m, 2H); 2.15–1.85(m, 3H)

3B



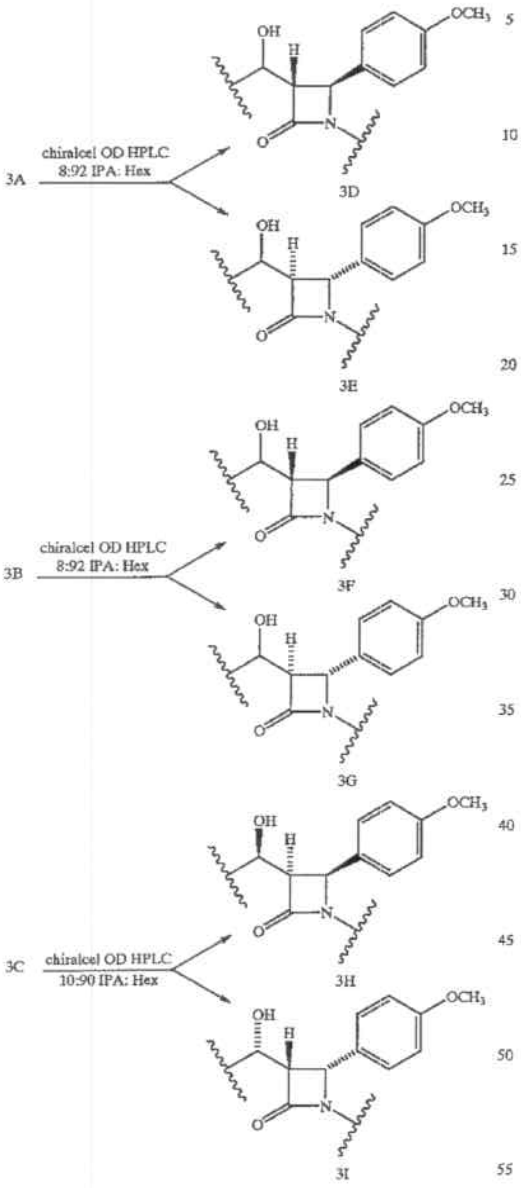
1H in $CDCl_3$:7.35–7.10(m, 11H); 7.08–6.99 (m, 1H); 6.89(d, J = 9 Hz, 2H); 5.09(d, J = 2.4 Hz, 1H); 4.26–4.14(m, 1H); 3.79(s, 3H); 3.21–3.14(m, 1H); 2.89–2.57(m, 2H); 2.10–1.85(m, 3H)

3C



1H in $CDCl_3$:7.30–7.00(m, 10H); 6.99 (d, J = 8 Hz, 2H); 6.83(d, J = 9 Hz, 2H); 5.12(d, J = 5.5 Hz, 1H); 3.82(s, 3H); 3.75–3.63(m, 1H); 3.52(dd, J = 9.5 Hz, 1H); 2.71–2.57(m, 1H); 2.49–2.33(m, 1H); 1.68–1.50(m, 1H); 1.47-1.31(m, 1H)

The 3A, 3B and 3C, diastereomers were further separated according to the following reaction scheme, wherein partial structures are shown:



(The following CD spectra data [θ] are all obtained in CH_3OH.)

3D) $[\theta]_{227nM}=+2.0\times10^4$ cm²/dM; $[\theta]_{241nM}=-4.6\times10^4$ cm²/dM. Elemental analysis calc for $C_{25}H_{25}NO_3$–0.25 H_2O: C 76.6; H 6.56 N 3.57. found: C 76.66; H 6.49; N 3.64.

3E) $[\theta]_{227nM}=-1.95\times10^4$ cm²/dM; $[\theta]_{241nM}=+4.45\times10^4$ cm²/dM. Elemental analysis calc for $C_{25}H_{25}NO_3$.0.5 H_2O: C 75.73; H 6.61; N 3.53. found: C 75.66; H 6.41; N 3.60.

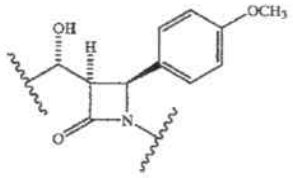
3F) $[\theta]_{226nM}=+1.97\times10^4$ cm²/dM; $[\theta]_{240nM}=-5.22\times10^4$ cm²/dM. Elemental analysis calc for $C_{25}H_{25}NO_3$: C 77.48; H 6.5–1; N 3.62. found: C 77.44; H 6.53; N 3.70.

3G) $[\theta]_{226nM}=-1.78\times10^4$ cm²/dM; $[\theta]_{241nM}=+4.78\times10^4$ cm²/dM (CIMS 388 M⁺H).

3H) $[\theta]_{226nM}=+2.24\times10^4$ cm²/dM; $[\theta]_{241nM}=-5.4\times10^4$ cm²/dM. $[\alpha]_D^{25}=-54.4°$ (2.5 mg/ml CH_3OH) Elemental analysis calc for $C_{25}H_{25}NO_3$: C 77.48; H 6.51; N 3.62. found: C 77.11; H 6.50; N 3.72.

3I) $[\theta]_{226nM}=-2.05\times10^4$ cm²/dM; $[\theta]_{241nM}=+5.2\times10^4$ cm²/dM. (CIMS 388 M⁺H).

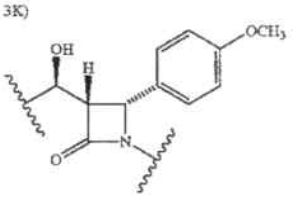
3J)



Add DEAD (0.11 ml) to a solution of compound 3H (132 mg), PPh_3 (0.18 g) and HCO_2H (39 ml) in THF (5 ml). Stir at room [temperatq] *temperature* overnight, then partition the reaction mixture between Et_2O and H_2O. Wash (brine) and dry ($MgSO_4$) the organic layer and concentrate to dryness. Flash chromatograph the residue using EtOAc:Hex (1:4) to obtain the formate ester. Dissolve this in CH_3OH and add 4 drops of conc. HCl. After 4 h, concentrate in vacuo and flash chromatograph the residue using EtOAc:Hex (1:3) to obtain 3J. $[\theta]_{224nM}=+2.54\times10^3$ cm²/dM;

$[\theta]_{239nM}=+5.70\times10^4$ cm²/dM; $[\alpha]_D^{20}=-157.6°$ (2.5 mg/ml CH_3OH)

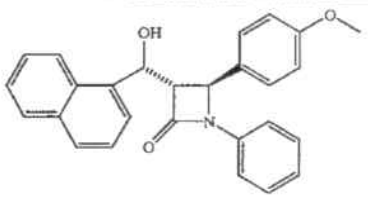
3K)



Using the procedure described for 3J, treat compound 3I to obtain 3K. $[\theta]_{222nM}=-3.4\times10^3$ cm²/dM; $[\alpha]_{240nM}=-5.6\times10^4$ cm²/dM. $[\alpha]_D^{20}=+167.2°$ (2.5 mg/ml CH_3OH)

Using the procedure described above for preparing compounds 3A and 3B, treat N-phenyl-4-(4-methoxyphenyl)-2-azetidinone with LICA followed by 2-naphthaldehyde to obtain the diastereomers 3L and 3M:

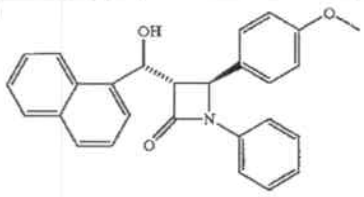
3L



mp 137–138° C.

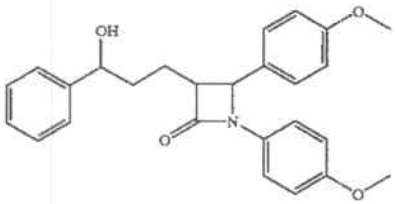
-continued

3M



mp 150–151° C.

EXAMPLE 4



Method 1:

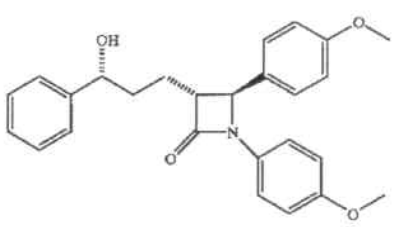
Step 1) To a refluxing solution of of 4-methoxyberizylidene anisidine (10.0 g, 41.5 mmol) and tributylamine (20.8 ml, 87 mmol) in toluene (100 ml), add 5-bromovaleroyl chloride (8.5 g, 43, mmol) in toluene (20 ml) dropwise over 2 h. Stir the reaction mixture at 80° C. for 12 h, cool to room temperature, wash 3× with 1 N HCl, 1× with water and dry the organic layer over $MgSO_4$. Purify by silica gel chromatography, eluting with ethyl acetate:hexane (4:1) to obtain 5.1 g of (3R, 4S)-1,4-bis(4-methoxyphenyl)-3-(3-bromoproyl)-2-azetidinone (relative stereochemistry), mp 70°–73° C., El (M^+) 404; J=2.3 Hz.

Step 2) To a solution of the product of step 1 (5.1 g, 12.6 mmol) in $(CH_3)_2SO$ (20 ml), add $(CH_3)_3N(O)$ (2.39 g, 31.9 mmol). Heat the mixture at 60° C. for 3 h, cool to room temperature, dilute with EtOAc, and wash 3× with water. Combine the aqueous fractions and extract with EtOAc. Combine the organic fractions and concentrate. Purify the crude product by silica gel chromatography, eluting with EtOAc:hexane (1:1) to obtain 1.4 g (3R, 4S)-1,4-bis-(4-methoxyphenyl)-2-oxo-3-azetidine-propanol (relative stereochemistry), an oil; El (M^+) 339; J=2.3 Hz.

Step 3) To a solution of the product of step 2 ([0.7134]*0.734* g, 2.2 mmol) in THF (4 ml) at 0° C., add phenylmagnesium bromide (2.4 ml, 2.4 mmol, 1.0 M in THF) over 0.25 h. After 1 h at 0° C., add water (5 ml), separate the layers, wash the organic layer 1 × with 1N HCl, dry with $MgSO_4$ and concentrate to an oil. Purify by silica gel chromatography, eluting with EtOAc:hexane (2:1) to obtain 0.372 g of the title compound (mix of diastereomers) as an oil. CI (M^+H) 418.

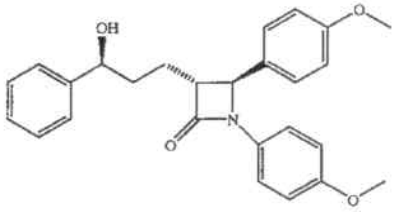
Separation of diastereomers: Apply the diastereomeric mixture from step 3 to a Chiralcel OD (Chiral Technologies Corp, Pa.) chromatography column, eluting with hexane:ethanol (9:1) to obtain enantiomerically pure (>98%) diastereomers as follows:

4A



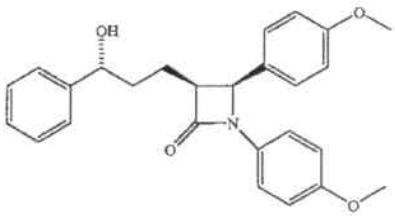
Oil;$[\alpha]_D^{22}$ = +8.3°, conc. = 3 mg/ml in MeOH; Cl($M+H$)418.J = 2.1Hz.

4B



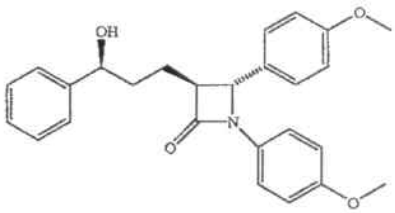
Oil;$[\alpha]_D^{22}$ = +33.1°, conc. = 3 mg/ml in MeOH; Cl($M+H$)418.J = 2.1Hz.

4C



Oil;$[\alpha]_D^{22}$ = -8.0°, conc. = 3 mg/ml in MeOH; Cl($M+H$)418.J = 2.1Hz.

4D



Oil;$[\alpha]_D^{22}$ = -29.5°, conc. = 3 mg/ml in MeOH; Cl($M+H$)418.J = 2.1Hz.

Method 2:

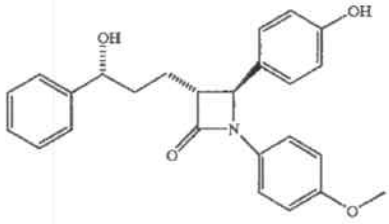
Step 1) To a solution of 1,4-(S)-bis(4-methoxyphenyl)-3-(3(R)-phenylpropyl)-2-azetidinone (5.04 g, 0.013 mole) in CCl_4 (20 ml) at 80° C., add NBS (2.76 g, 0.0155 mole) and benzoyl peroxide (0.24 g, 1.0 mmole) in three equal portions over 1 h. Follow the reaction by TLC (4:1 hexane:EtOAc). Cool the reaction to 22° C., add $NaHSO_4$, separate the layers and wash the organic layer 3× with water. Concentrate the organic layer to obtain the crude product.

CI (M^+H) 480; ^1H in $CDCl_3$ δ PhC<u>H</u>(OH)=5.05 ppm.

Step 2) Dissolve the crude product of Step 1 in CH_2Cl_2 (30 ml) and add 40% n-BuNOC(O)CF_3 in water (30 ml). Reflux the biphasic reaction for 24 h, cool, separate the layers and wash the organic layer 6× with water. Concentrate the organic layer to dryness and immediately redissolve the residue in ethanol saturated with NH_3 (10 ml). After 1 h, concentrate the reaction mixture and partially purify by silica gel chromatography. Further purify by HPLC to obtain a 1:1 mixture of compounds 4A and 4B. The mixture can be further purified on a Chiracel OD column to obtain 4A and 4B separately as characterized above.

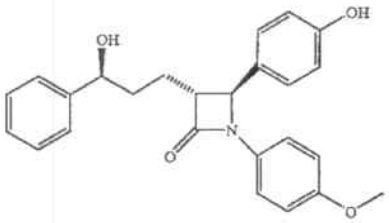
Using the procedure described in Example 4, Method 2, with 4(S)-(4-acetoxyphenyl)-3(R)-(3-phenylpropyl)-1-(4-methoxy-phenyl)-2-azetidinone as the starting material, prepare the following compounds:

4E



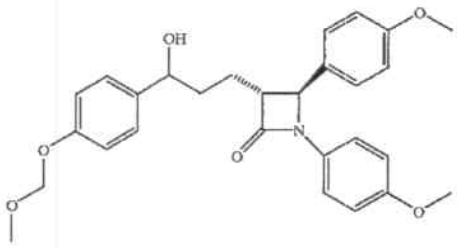
mp 87–90° C.;
HRMS calc'd for $C_{25}H_{25}NO_4$ = 403.1797, found 403.1785;
^1H in $CDCl_3$ δPhCH(OH) = 4.82 ppm.

4F



HRMS calc'd for $C_{25}H_{25}NO_4$ = [403.1787, found 403.1785]; 403.1797, found 403.1787;
^1H in $CDCl_3$ δPhCH(OH) = 4.78

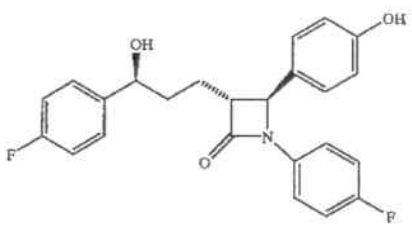
EXAMPLE 5



To a solution of the product of step 2 of Example 4 (0.230 g, 0.68 mmol) in THF (2 ml), add the reagent derived from treatment of 4-methoxymethylphenyl bromide (0.159 g, 0.736 mmol) in THF (4 ml) at −78° C. with sec-butyllithium (0.6 ml, 0.78 mol, 1.3M in hexanes), followed by $CeCl_3$ (0.186 g, 0.75 mmol). After 4 h, extract the product and purify by chromatography in a manner similar to that described in step 3 of Example 4 to obtain 0.05 g of the title compound (mix of diastereomers) as an oil. CI (M^+H) 478.

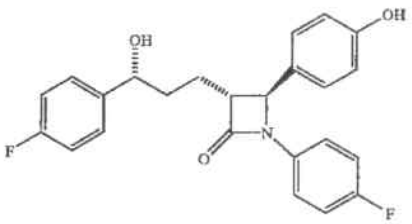
EXAMPLE 6

6A



and

6B



Step 1): To a solution of (S)-4-phenyl-2-oxazolidinone (41 g, 0.25 mol) in CH_2Cl_2 (20 ml), add 4-dimethylaminopyridine (2.5 g, 0.02 mol) and triethylamine (84.7 ml, 0.61 mol) and cool the reaction to 0° C. Add methyl-4-(chloroformyl)butyrate (50 [9] *g*, 0.3 mol) as a solution in CH_2Cl_2 (375 ml) dropwise over 1 h, and allow the reaction to warm to 22° C. After 17 h, add water and H_2SO_4 (2N, 100 ml), separate the layers, and wash the organic layer sequentially with NaOH (10%). NaCl (sat'd) and water. Dry the organic layer over $MgSO_4$ and concentrate to obtain a semicrystalline product.

Step 2): To a solution of $TiCl_4$ (18.2 ml, 0.165 mol) in CH_2Cl_2 (600 ml) at 0° C., add titanium isopropoxide (16.5 ml, 0.055 mol). After 15 min, add the product of Step 1 (49.0 9, 0.17 mol) as a solution in CH_2Cl_2 (100 ml). After 5 min., add diisopropylethylamine (DIPEA) (65.2 ml, 0.37 mol) and stir at 0° C. for 1 h, cool the reaction mixture to −20° C., and add 4-benzyloxybenzylidine(4-fluoro)aniline (114.3 g, 0.37 mol) as a solid. Stir the reaction vigorously for 4 h at −20° C., add acetic acid as a solution in CH_2Cl_2 dropwise over 15 min, allow the reaction to [warnr] *warm* to 0° C., and add H_2SO_4 (2N). Stir the reaction an additional 1 h, separate the layers, wash with water, separate and dry the organic layer. Crystallize the crude product from ethanol/water to obtain the pure intermediate.

Step 3): To a solution of the product of Step 2 (8.9 g, 14.9 mmol) in toluene (100 ml) at 50° C., add N,O-bis (trimethylsilyl)acetamide (BSA) (7.50 ml, 30.3 mmol). After 0.5 h, add solid TBAF (0.39 g, 1.5 mmol) and stir the reaction at 50° C. for an additional 3 h. Cool the reaction mixture to 22° C., add CH_3OH (10 ml), wash the reaction mixture with HCl (1N), $NaHCO_3$ (1N) and NaCl (sat'd), and dry the organic layer over $MgSO_4$.

Step 4): To a solution of the product of Step 3 (0.94 g, 2.2 mmol) and CH_3OH (3 ml), add water (1 ml) and $LiOH.H_2O$ (102 mg, 2.4 mmole). Stir the reaction at 22° C. for 1 h and add additional $LiOH.H_2O$ (54 mg, 1.3 mmole). After a total of 2 h, add HCl (1N) and EtOAc, separate the layers, dry the

organic layer and concentrate in vacuo. To a solution of resultant product (0.91 g, 2.2 mmol) in CH_2Cl_2 at 22° C., add ClCOCOCl (0.29 ml, 3.3 mmol) and stir for 16 h. Remove the solvent in vacuo.

Step 5): To an efficiently stirred suspension of 4-fluorophenylzinc chloride (4.4 mmol) prepared from 4-fluorophenylmagnesium bromide 5 (1M in THF, 4.4 ml, 4.4 mmol) and $ZnCl_2$ (0.6 g, 4.4 mmol) at 4° C., add tetrakis(triphenylphosphine)palladium (0.25 g, 0.21 mmol) and the product of Step 4 (0.94 g, 2.2 mmol) as a solution in THF (2 ml). Stir the reaction for 1 h at 0° C. and then for 0.5 h at 22° C. Add HCl (1N, 5 ml) and extract with EtOAc. Concentrate the organic layer to an oil and purify by silica gel chromatography to obtain 1-(4-fluorophenyl)-4(S)-(4-hydroxyphenyl)-3(R)-(3-oxo-3-phenylpropyl)-2-azetidinone:

HRMS calc'd for $C_{24}H_{19}F_2NO_3$=408.1429, found 408.1411.

Step 6): To the product of Step 5 (0.95 g, 1.91 mmol) in THF (3 ml), add (R)-tetrahydro-1-methyl-3,3-diphenyl-1H, 3H-pyrrolo-[1,2-c][1,3,2]oxazaborole (120 mg, 0.43 mmol) and cool the mixture to −20° C. After 5 min, add borohydride-dimethylsulfide complex (2M in THF: 0.85 ml, 1.7 mmol) dropwise over 0.5 h. After a total of 1.5 h, add CH_3OH followed by HCl (1 N) and extract the reaction mixture with EtOAc to obtain 1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl)]-4(S)-[4-(phenylmethoxy)phenyl]-2-azetidinone (compound 6A-1) as an oil. ^1H in $CDCl_3$ δ H3=4.68, J=2.3 Hz. CI (M^+H) 500.

Use of (S)-tetra-hydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo-[1,2-c][1,3,2] oxazaborole gives the corresponding 3(R)-hydroxypropyl azetidinone (compound 6B-1). ^1H in $CDCl_3$ δ H3=4.69, J=2.3 Hz. CI (M^+H) 500.

To a solution of compound 6A-1 (0.4 g, 0.8 mmol) in ethanol (2 ml), add 10% Pd/C (0.03 g) and stir the reaction under a pressure (60 psi) of H_2 gas for 16 h. Filter the reaction mixture and concentrate the solvent to obtain compound 6A. Mp 164°–166° C.; CI (M^+H) 410.

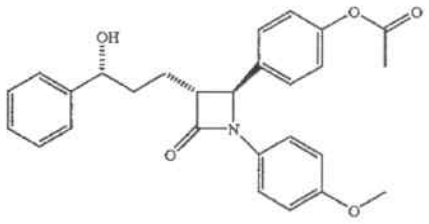
$[\alpha]_D^{25}$=−28.1° (c 3, CH_3OH). Elemental analysis calc'd for $C_{24}H_{21}F_2NO_3$; C 70.41; H 5.17; N 3.42; found C 70.25; H 5.19; N 3.54.

Similarly treat compound 6B-1 to obtain compound 6B. Mp 129.5°–132.5° C.; CI (M^+H) 410. Elemental analysis calc'd for $C_{24}H_{21}F_2NO_3$: C 70.41; H 5.17; N 3.42; found C 70.30; H 5.14; N 3.52.

Step 6') (Alternative): To a solution of the product of Step 5 (0.14 g, 0.3 mmol) in ethanol (2 ml), add 10% Pd/C (0.03 g) and stir the reaction under a pressure (60 psi) of H_2 gas for 16 h. Filter the reaction mixture and concentrate the solvent to afford a 1:1 mixture of compounds 6A and 6B.

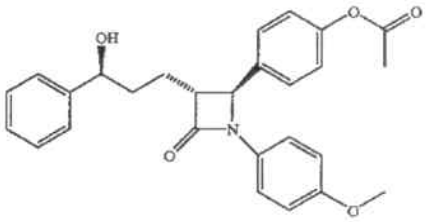
Using appropriate starting materials and following the procedure of steps 1–6, prepare the following compounds:

6C



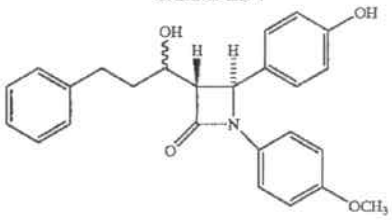
CI(M+H)446;
HRMS calc'd for $C_{27}H_{27}NO_3$ = 445.1904, found 445.1890

6D



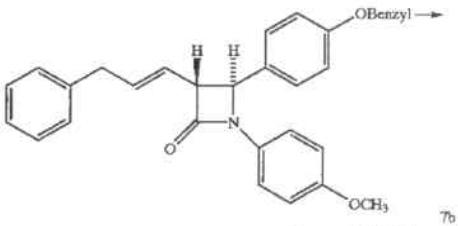
CI(M+H)446;
HRMS calc'd for $C_{25}H_{25}NO_4$ = 445.1904, found 445.1911

EXAMPLE 7

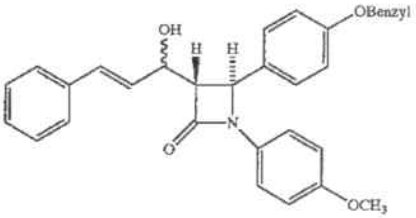


7a

Step 1):



7b



To a solution of 7a (1.0 g, 2.1 mmol) in dioxane (10 ml), add SeO_2 (1.33 g, 11.98 mmol) and water [(25 ml, 14 mmol),] *(0.25 ml, 14 mmol)*, and heat the reaction to 100° C. After 1

h, cool the reaction to room temperature and isolate by extraction the crude product as a diastereomeric mixture (1:2) of alcohols 7b-A and 7b-B. Purify by HPLC on a Dynamax silica column to separate diastereomers 7b-A and 7b-B.

Diastereomer 7b-A (R): oil; J_{34}=2.3 Hz, δ C H(OH)=4.86 (t); HRMS $C_{32}H_{29}NO_4$ calc.: 491.2097; found: 491.2074.

Diastereomer 7b-E (S): oil; J_{34}=2.3 Hz, δ C H(OH)=5.06 (t); HRMS $C_{32}H_{29}NO_4$ calc.: 491.2097; found: 491.2117.

Step 2): To a solution of diastereomer A from step 1 (58 mg, 0.12 mmol) in EtOAc (2 ml), add 10% Pd on carbon (20 mg) and stir at 22° C. under H_2 gas (14 psi) for 12 h. Filter and concentrate to obtain the title compound as a semisolid, m.p. 90°–92° C. J_{34}=2.3 Hz, δ CH(OH)=4.1 (m); HRMS $C_{25}H_{25}NO_4$ calc: 403.1783; found: 403.1792.

EXAMPLE 8

To a solution of the product of Example 4A (90 mg, 0.2 mmol) in CH_2Cl_2, add acetyl chloride (80 mg, 1.0 mmol) and pyridine (8 mg, 0.1 mmol) and stir at room temperature for 1 h. Add water, separate the layers and isolate the corresponding acetoxy compound, 8A. In a similar manner, treat the products of Examples 4B, 6B and 6A to obtain the following compounds 8B, 8° C. and 8D, respectively:

8A: 1,4(S)-bis(4-methoxyphenyl)-3(R)-(3(R)-acetoxy-3-phenylpropyl)-2-azetidinone. CI (M^+H) 460; HRMS $C_{28}H_{29}NO_5$ calc.: 459.2044; found: 459.2045.

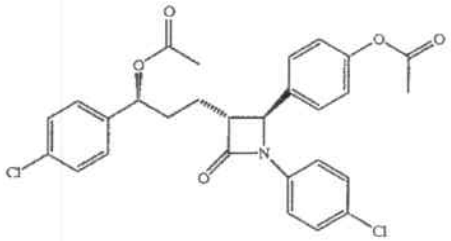
8B: 1,4(S)-bis(4-methoxyphenyl)-3(R)-(3(S)-acetoxy-3-phenylpropyl)-2-azetidinone. CI (M^+H) 460; HRMS $C_{28}H_{29}NO_5$ calc.: 459.2044; found 459.2048.

8C: 4(S)-(4-acetyloxyphenyl)-3(R)-(3(R)-acetyloxy-3-(4-fluorophenyl)propyl)-1-(4-fluorophenyl)-2-azetidinone. FAB M:S 493.4; HRMS $C_{28}H_{25}F_2NO_5$ calc.: 493.1695; found: 493.1701.

8D: 4(S)-(4-acetyloxyphenyl)-3(R)-(3(S)-acetyloxy-3-(4-fluorophenyl)propyl)-1-(4-fluorophenyl)-2-azetidinone. FAB MS 493.4; HRMS $C_{28}H_{25}F_2NO_5$ calc.: 493.1695; found: 493.1694.

Using appropriate starting materials in the procedure of Example 6, prepare 1-(4-chlorophenyl)-3(R)-(hydroxy-3-(4-chlorophenylpropyl)-4(S)-(4-hydroxyphenyl)-2-azetidinone. Using the procedure of Example 8, prepare the following diacetates 8E and 8F:

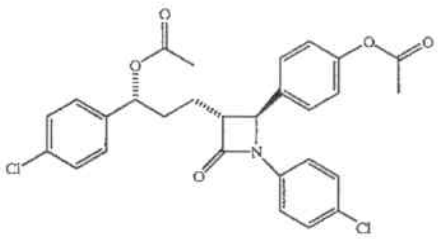
8E



CI(M + H)527;
^{1}H $CDCl_3$δ H3' = 4.65

-continued

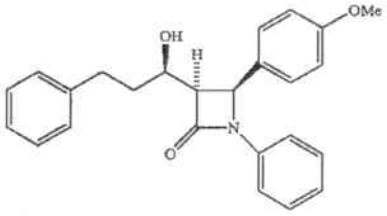
8F



CI(M + H)527;
^{1}H $CDCl_3$δ H3' = 4.67

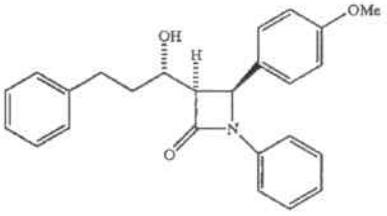
EXAMPLE 9

3H



and

3K



Step 1:

Add pyridinium chlorochromate (2.4 g, 11 mmoles) and CH_3CO_2Na (approx. 20 mg) to a solution of 1-phenyl-3-(3-phenyl-1-hydroxypropyl)-4-(4-methoxyphenyl)-2-azetidinone (2.35 g, 6.1 mmoles) in CH_2Cl_2. Stir at room temperature for 18 h, then add silica gel (40 g) and concentrate to dryness. Flash chromatograph the residue using EtOAc:Hex (1:4) to obtain an oil. (1.98 g, yield=85%). ^{1}H NMR 2.85–2.95 (m, 3H), 3.15 (m, 1H), 3.80 (s, 3H), 4.10 (d, 1H, J 2.6), 5.42 (1H, d, 6.85 (dd, 2H, J 2.8), 7.05 (m, 1H), 7.2–7.35 (m, 11H).

Step 2:

To a solution of the product of Step 1 (1.78 g, 4.62 mmoles) in THF at −10° C., add NaH (115 mg, 4.8 mmoles). After 15 min, add NBS (865 mg, 4.85 mmoles) and stir for 20 min., then add 1N HCl and partition between EtOAc and brine. Separate the organic layer, dry ($MgSO_4$) and concentrate to give an oil. Flash chromatograph the oil using EtOAc:Hex (1:10) to collect first 9a as a foamy solid (830 mg, y=39%, FAB MS 466/464, M+H), and then 9b as a colorless solid (1.1 g, y=51%, FAB MS 466/464, M+H).

Step 3a:

Add $Mg(OCOCF_3)_2$.CF_3CO_2H (7.3 ml of 1M solution is Et_2O.) to a solution of 9a (0.68 g, 1.46 mmoles) in THF (5

ml) at −50° C. Stir the reaction 5 min., then add t-Bu—NH_2-BH_3 (254 mg, 2.92 mmole). After 15 min., allow the reaction to warm to 0° C. over 20 min., add 1N HCl and concentrate in vacuo. Partition the residue between EtOAc and brine. Concentrate the organic layers and dissolve the resultant oil in CH_2Cl_2:CH_3OH (1:1) and add ethanolamine (approx 2 mmoles). After 15 min., concentrate the reaction mixture and partition the residue with EtOAc:1N HCl. Wash (brine) and dry ($MgSO_4$) the organic layer to obtain an oil. Purify this oil by flash chromatography using EtOAc:Hex (1:4) to obtain compound 9a-1, a colorless solid, as a 4:1 mix of diastereomers. 0.52 g, y=76%, SIMS 468/466 (M+H).

Step 3b:

Using compound 9b as the starting material, use a procedure similar to Step 3a with CH_2Cl_2 as solvent for the preparation of 9b-1 in 80% yield as a 13:1 mixture of diastereomers (SIMS 468/466 M+H).

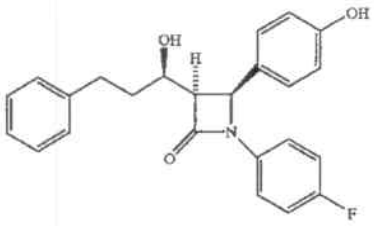
Step 4a:

Add a solution of 9a-1 (0.27 g, 0.58 mmoles) and AIBN (18 mg, 0.12 mmole) in toluene (40 ml) dropwise over 40 min. to a solution of $(TMS)_3SiH$ (1.0 ml) in toluene at 80° C. for 1.5 h. Cool and concentrate the reaction mixture, dissolve the residue in CH_3CN and wash 3× with hexane. Concentrate the CH_3CN layer to give the title compound as a racemic mixture (0.25 g). Purify this oil by HPLC using a Chiralcel OD column to obtain 3H (major) and 3J (minor).

Step 4b:

Use the procedure of Step 4a, starting with compound 9b-1 to obtain an oil. Purify this by flash chromatography using EtOAc:Hex (1:3) to collect the racemic title compound (y=70%). Purify this oil by HPLC using a Chiralcel OD column to obtain 3J (major) and 3H (minor).

EXAMPLE 10



Step 1:

Follow the procedure of Example 3, using 1-(4-fluorophenyl-4-(4-t-butyldimethylsilyloxyphenyl)-2-azetidinone to obtain 1-(4-fluorophenyl-3-(3-phenyl-1-hydroxypropyl) 4-(4-t-butyldimethylsilyl-oxyphenyl)-2-azetidinone.

Step 2:

Treat a solution of the cis-azetidinone of Step 1 (0.25 g) in [CH3CN] CH_3CN (21 ml) with 48% aqueous HF (2.5 ml). After 18 h, dilute the reaction mixture with cold H_2O and extract with Et_2O. Wash (2× H_2O, dilute $NaHCO_3$ and brine), dry ($MgSO_4$) and concentrate the Et_2O layer. Crystallize the residue from EtOAc:hexane (1:2) to obtain the title compound as colorless needles (123 mg, y=64%), mp 168°–171° C. Elemental analysis calc for $C_{24}H_{22}O_3FN$: C 73.64; H 5.66; N 3.58. found C 73.32; H 5.65; N 3.68.

The following formulations exemplify some of the dosage of this invention. In each the term "active compound" designates a compound of formula I.

EXAMPLE A

Tablets

No.	Ingredient	mg/tablet	mg/tablet
1	Active Compound	100	500
2	Lactose USP	122	113
3	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4	Corn Starch, Food Grade	45	40
5	Magnesium Stearate	3	7
	Total	300	700

Method of Manufacture

Mix Item Nos. 1 and 2 in suitable mixer for 10–15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., ¼', 0.63 cm) if necessary. Dry the [cl] *d*amp granules. Screen the dried granules if necessary and mix with Item No. 4 and mix for 10–15 minutes. Add Item No. 5 and mix for 1–3 minutes. Compress the mixture to appropriate size and weight on a suitable tablet machine.

EXAMPLE B

Capsules

No.	Ingredient	mg/tablet	mg/tablet
1	Active Compound	100	500
2	Lactose USP	105	123
3	Corn Starch, Food Grade	40	70
4	Magnesium Stearate NF	4	7
	Total	250	700

Method of Manufacture

Mix Item Nos. 1, 2 and 3 in a suitable blender for 10–15 minutes. Add Item No. 4 and mix for 1–3 minutes. Fill the mixture suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

Representative formulations comprising a cholesterol biosynthesis inhibitor are well known in the art. It is contemplated that where the two active ingredients are administered as a single composition, the dosage forms disclosed above for substituted azetidinone compounds may readily be modified using the knowledge of one skilled in the art.

Using the test procedures described above, the following in vivo data were obtained for the exemplified compounds. Data is reported as percent change (i.e., percent reduction in cholesterol esters) versus control, therefore, negative numbers indicate a positive lipid-lowering effect.

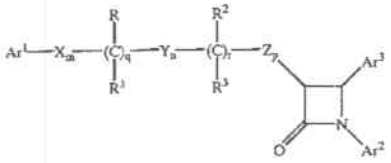
	% Reduction		
Ex. #	Serum Cholest.	Cholest. Esters	Dose mg/kg
1A	−23	0	50
1B	−15	−39	50

-continued

Ex. #	% Reduction Serum Cholest.	Cholest. Esters	Dose mg/kg
1C	14	0	50
2	0	0	50
3A	−31	−69	50
3C	−60	−92	50
3D	−17	−61	10
3E	0	0	10
3F	−29	−77	10
3G	−16	−38	10
3H	−41	−86	10
3I	0	−22	10
3J	0	0	3
3K	0	0	10
3L	−15	−21	10
3M	0	−22	10
4A	0	−54	5
4B	−37	−89	8
4C	−12.5	0	3
4D	9	0	7
4E	0	−46	3
4F	−29	−95	3
5	0	−64	10
6A	−59	−95	1
6A-1	−43	−93	1
6B	−40	−92	3
6C	0	−48	3
6D	−46	−95	10
8A	0	−44	3
8B	−50	−95	3
8C	−14	−37	1
8D	−49	−98	1
8E	−22	−66	3
8F	−43	−94	1
10	−26	−77	3

We claim:

1. A compound represented by the formula



or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 and Ar^2 are independently selected from the group consisting of aryl and R^4-substituted aryl;

Ar^3 is aryl or R^5-substituted aryl;

X, Y and Z are independently selected from the group consisting of —CH_2—, —CH(lower alkyl)- and —C(dilower alkyl)-;

R and R^2 are independently selected from the group consisting of —OR^6, —$O(CO)R^6$, —$O(CO)OR^9$ and —$O(CO)NR^6R^7$;

R^1 and R^3 are independently selected from the group consisting of hydrogen, lower alkyl and aryl;

q is 0 or 1; r is 0 or 1; m, n and p are independently 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5;

R^4 is 1–5 substituents independently selected from consisting of lower alkyl, —OR^6, —$O(CO)R^6$, —$O(CO)OR^9$, —$O(CH_2)_{1-5}OR^6$, —$(CO)NR^6R^7$, —NR^6R^7, —$NR^6(CO)R^7$, —$NR^6(CO)OR^9$, —$NR^6(CO)NR^7R^8$, —$NR^6SO_2R^9$, —$COOR^6$, —$CONR^6R^7$, -COR^6, -$SO_2NR^6R^7$, $S(O)_{0-2}R^9$, —$O(CH_2)_{1-10}$—$COOR^6$, —$O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$, —CH═CH—$COOR^6$, —CF_3, —CN, —NO_2 and halogen;

R^5 is 1–5 substituents independently selected from the group consisting of —OR^6, —$O(CO)R^6$, —$O(CO)OR^9$, —$O(CH_2)_{1-5}OR^6$, —$(CO)NR^6R^7$, —NR^6R^7, —$NR^6(CO)R^7$, —$NR^6(CO)OR^9$, —$NR^6(CO)NR^7R^8$, —$NR^6SO_2R^9$, —$COOR^6$, —$CONR^6R^7$, —COR^6, —$SO_2NR^6R^7$, $S(O)_{0-2}R^9$, —$O(CH_2)_{1-10}$—$COOR^6$, —$O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$ and —CH═CH—$COOR^6$;

R^6, R^7 and R^8 are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

R^9 is lower alkyl, aryl or aryl-substituted lower alkyl.

2. A compound of claim 1 wherein Ar^1 is phenyl or R^4-substituted phenyl, Ar^2 is phenyl or R^4-substituted phenyl and Ar^3 is R^5-substituted phenyl.

3. A compound of claim 2 wherein Ar^1 is R^4-substituted phenyl wherein R^4 is halogen; Ar^2 is R^4-substituted phenyl wherein R^4 is halogen or —OR^5, wherein R^6 is lower alkyl or hydrogen; and Ar^3 R^5-substituted phenyl, wherein R^5 is —OR^6, wherein R6 is lower alkyl or hydrogen.

4. A compound of claim 1 wherein X, Y, and Z are each —CH_2—; R^1 and R^3 are each hydrogen; R and R^2 are each —OR^6, wherein R^6 is hydrogen; and the sum of m, n, p, q and r is 2, 3 or 4.

5. A compound of claim 1 wherein m, n and r are each zero, q is 1 and p is 2.

6. A compound of claim 1 wherein p, q and n are each zero, r is 1 and m is 2 or 3.

7. A compound selected from the group consisting of

rel 3(R)-(2(R)-hydroxy-2-phenylethyl)-4(R)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

rel 3(R)-(2(R)-hydroxy-2-phenylethyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

3(S)-(1(S)-hydroxy-3-phenylpropyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

3(S)-(1(R)-hydroxy-3-phenylpropyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

3(R)-(1(R)-hydroxy-3-phenylpropyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

rel-3(R)-[(S)-hydroxy-(2-naphthalenyl)methyl]-4(S)-(4-methoxyphenyl)-1-phenyl)-1-phenyl-2-azetidinone;

rel-3(R)-[(R)-hydroxy-(2-naphthalenyl)methyl]-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

3(R)-(3(R)-hydroxy-3-phenylpropyl)-1,4(S)-bis-(4-methoxyphenyl-2-azetidinone;

3(R)-(3(S)-hydroxy-3-phenylpropyl)-1,4(S)-bis-(4-methoxyphenyl-2-azetidinone;

4(S)-(4-hydroxyphenyl)-3(R)-(3(R)-hydroxy-3-phenylpropyl-1-(4-methoxyphenyl)-2-azetidinone;

4(S)-(4-hydroxyphenyl)-3(R)-(3(S)-hydroxy-3-phenylpropyl-1-(4-methoxyphenyl)-2-azetidinone;

rel 3(R)-[3(RS)-hydroxy-3-[4-methoxymethoxy)-phenyl]propyl]-1,4(S)-bis-(4-methoxyphenyl)-2-azetidinone;

1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl)]-4(S)-(4-hydroxyphenyl)-2-azetidinone;

1-(4-fluorophenyl)-3(R)-[3(R)-(4-fluorophenyl)-3-hydroxypropyl)]-4(S)-(4-hydroxyphenyl)-2-azetidinone;

4(S)-[4-(acetyloxy)phenyl]-3(R)-(3(R)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone;

4(S)-[4-(acetyloxy)phenyl]-3(R)-(3(S)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone;

1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl)]-4(S)-[4-(phenylmethoxy)phenyl]-2-azetidinone;

3(R)-[3(R)-acetyloxy)-3-phenylpropyl]-1,4(S)-bis-(4-methoxyphenyl)-2-azetidinone;

3(R)-[3(S)-acetyloxy)-3-phenylpropyl]-1,4(S)-bis-(4-methoxyphenyl)-2-azetidinone;

3(R)-[3(R)-(acetyloxy)-3-(4-fluorophenyl)propyl]-4(S)-[4-(acetyloxy)phenyl]-1-(4-fluorophenyl)-2-azetidinone;

3(R)-[3(S)-(acetyloxy)-3-(4-fluorophenyl)propyl]-4(S)-[4-(acetyloxy)phenyl]-1-(4-fluorophenyl)-2-azetidinone;

3(R)-[3(R)-(acetyloxy)-3-(4-chlorophenyl)propyl]-4(S)-[4-(acetyloxy)phenyl]-1-(4-chlorophenyl)-2-azetidinone;

3(R)-[3(S)-(acetyloxy)-3-(4-chlorophenyl)propyl]-4(S)-[4-(acetyloxy)phenyl]-1-(4-chlorophenyl)-2-azetidinone; and

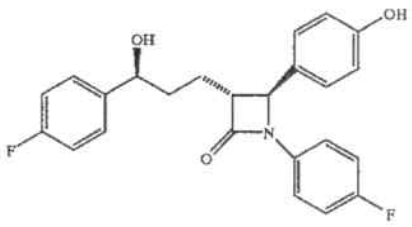
rel 1-(4-fluorophenyl)-4(S)-(4-hydroxyphenyl)-3(1R)-(1(R)-hydroxy-3-phenylpropyl)-2-azetidinone.

8. A pharmaceutical composition for the treatment or prevention of [atherosclerosis], *atherosclerosis* or for the reduction of plasma cholesterol levels, comprising an effective amount of a compound of claim **1** in a pharmaceutically acceptable carrier.

9. A method of treating or preventing atherosclerosis or reducing plasma cholesterol levels comprising administering to a mammal in need of such treatment an effective amount of a compound of claim **1**.

10. A compound comprising 1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl)]-4(S)-4-(hydroxyphenyl)-2-azetidinone or a pharmaceutically acceptable salt thereof.

11. A compound represented by the formula:



12. A pharmaceutical composition for the treatment or prevention of atherosclerosis, or for the reduction of plasma cholesterol levels, comprising an effective amount of a compound according to claims 10 or 11 in a pharmaceutically acceptable carrier.

13. A method of treating or preventing atherosclerosis or reducing plasma cholesterol levels comprising administering to a mammal in need of such treatment an effective amount of a compound according to claims 10 or 11.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : RE 37,721 E
DATED : May 28, 2002
INVENTOR(S) : Stuart B. Rosenblum, Sundeep Dugar, Duane A. Burnett, John W. Clader and Brian A. McKittrick

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,
Item [22], delete "Filed: **June 15, 2000**" and insert therein:
-- PCT Filed: **September 14, 1994** --;
Item [86], insert therein: "PCT No.: **PCT/US94/10099**
§371(c)(1),
(2), (4) Date: **Mar. 18, 1996**";
Item [87], and insert therein: -- PCT Pub. No.: **WO95/08532**
PCT Pub. Date: **Mar. 30, 1995** --

Signed and Sealed this

Fifth Day of November, 2002

Attest:

Attesting Officer

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

Exhibit B

US005846966A

United States Patent [19]

Rosenblum et al.

[11] **Patent Number: 5,846,966**

[45] **Date of Patent: Dec. 8, 1998**

[54] **COMBINATIONS OF HYDROXY-SUBSTITUTED AZETIDINONE COMPOUNDS AND HMG COA REDUCTASE INHIBITORS**

[75] Inventors: **Stuart B. Rosenblum**, West Orange; **Sundeep Dugar**, Bridgewater; **Duane A. Burnett**, Fanwood; **John W. Clader**, Cranford; **Brian A. McKittrick**, Bloomfield, all of N.J.

[73] Assignee: **Schering Corporation**, Kenilworth, N.J.

[21] Appl. No.: **953,825**

[22] Filed: **Oct. 14, 1997**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 617,751, Mar. 18, 1996, Pat. No. 5,767,115, which is a continuation-in-part of Ser. No. 257,593, Jun. 9, 1994, Pat. No. 5,631,365, which is a continuation-in-part of Ser. No. 102,440, filed as PCT/US94/10099 Sep. 14, 1994, abandoned.

[51] **Int. Cl.**[6] **A61K 31/395**; A61K 31/40; A61K 31/35; A61K 31/21

[52] **U.S. Cl.** **514/210**; 514/423; 514/451; 514/460; 514/510; 514/824

[58] **Field of Search** 514/210, 423, 514/451, 460, 510, 824

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,375,475	3/1983	Willard et al.	424/279
4,983,597	1/1991	Yang et al.	514/216
5,099,034	3/1992	Yoshida	562/579
5,350,868	9/1994	Yoshida	562/579
5,631,365	5/1997	Rosenblum et al.	540/200
5,661,145	8/1997	Davis	514/210

FOREIGN PATENT DOCUMENTS

199630	10/1986	European Pat. Off. .
264231	4/1988	European Pat. Off. .
337549	10/1989	European Pat. Off. .
93/02048	2/1993	WIPO .
WO94/17038	8/1994	WIPO .

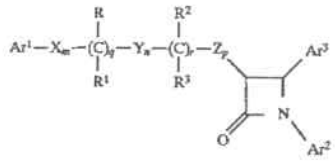
OTHER PUBLICATIONS

Ram et al, *Indian J. Chem., Sect B, 29B,* 12 (1990), pp. 1134–1137.
Hoekman et al, *J. Agric. Food Chem., 30* (1982), pp. 920–924.
Durst et al, *Can. J. Chem., 50* (1972), pp. 3196–3201.
Otto et al, *Liebigs Ann. Chem.,* (1983), pp. 1152–1161.
Panfil, et al., *Heterocycles, 24,* 6 (1986), pp. 1609–1617.
Schnitzer–Polokoff, et al, *Comp. Biochem. Physiol., 99A* (1991), pp. 665–670.
Witzum, *Circulation, 80,* 5 (1989), pp.1101–1114.
Illingworth, *Drugs, 36*(Supp. 3) (1988), pp. 63–71.
Allain, et al., *Clin. Chem., 20,* (1974), pp. 470–475.
Horie, et al, *Atherosclerosis, 88* (1991), pp. 183–192.
Baxter, et al, *J. Biological Chem., 267,* 17 (1992), pp. 11705–11708.
Current Drugs: Anti–Atherosclerotic Agents—Summary Factfile, May, 1992.
Georg et al, *Tet. Letters, 26,* 45 (1985), pp. 3903–3906.
Hart et al, *Tet. Letters, 26,* 45 (1985), pp. 5493–5496.

Primary Examiner—Kimberly Jordan
Attorney, Agent, or Firm—Anita W. Magatti

[57] **ABSTRACT**

Hydroxy-substituted azetidinone hypocholesterolemic agents of the formula



or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 and Ar^2 are aryl or R^4-substituted aryl;

Ar^3 is aryl or R^5-substituted aryl;

X, Y and Z are —CH_2—, —CH(lower alkyl)— or —C(dilower alkyl)—;

R and R^2 are —OR^6, —$O(CO)R^6$, —$O(CO)OR^9$ or —$O(CO)NR^6R^7$;

R^1 and R^3 are H or lower alkyl;

q is 0 or 1; r is 0 or 1; m, n and p are 0–4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1–6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1–5;

R^4 is selected from lower alkyl, R^5, —CF_3, —CN, —NO_2 and halogen;

R^5 is selected from —OR^6, —$O(CO)R^6$, —$O(CO)OR^9$, —$O(CH_2)_{1-5}OR^6$, —$O(CO)NR^6R^7$, —NR^6R^7, —$NR^6(CO)R^7$, —$NR^6(CO)OR^9$, —$NR^6(CO)NR^7R^8$, —$NR^6SO_2R^9$, —$COOR^6$, —$CONR^6R^7$, —COR^6, —$SO_2NR^6R^7$, $S(O)_{0-2}R^9$, —$O(CH_2)_{1-10}$—$COOR^6$, —$O(CH_2)_{1-10}CONR^6R^7$, —(lower alkylene)$COOR^6$ and —CH=CH—$COOR^6$;

R^6, R^7 and R^8 are H, lower alkyl, aryl or aryl-substituted lower alkyl;

R^9 is lower alkyl, aryl or aryl-substituted lower alkyl;

are disclosed, as well as a method of lowering serum cholesterol by administering said compounds, alone or in combination with a cholesterol biosynthesis inhibitor, pharmaceutical compositions containing them, and a process for preparing them.

10 Claims, No Drawings

COMBINATIONS OF HYDROXY-SUBSTITUTED AZETIDINONE COMPOUNDS AND HMG COA REDUCTASE INHIBITORS

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a division of U.S. application Ser. No. 08/617,751, filed Mar. 18, 1996, now U.S. Pat. No. 5,767,115, which is the U.S. national application corresponding to International Application No. PCT/US 94/10099, filed Sep. 14, 1994 and designating the U.S., which PCT application is in turn a continuation-in-part of U.S. application Ser. No. 08/257,593, filed Jun. 9, 1994, U.S. Pat. No. 5,631,365, which is a continuation-in-part of U.S. application Ser. No. 08/102440, filed Sep. 21, 1993, abandoned.

BACKGROUND OF THE INVENTION

The present invention relates to hydroxy-substituted azetidinones useful as hypocholesterolemic agents in the treatment and prevention of atherosclerosis, and to the combination of a hydroxy-substituted azetidinone of this invention and a cholesterol biosynthesis inhibitor for the treatment and prevention of atherosclerosis. The invention also relates to a process for preparing hydroxy-substituted azetidinones.

Atherosclerotic coronary heart disease (CHD) represents the major cause for death and cardiovascular morbidity in the western world. Risk factors for atherosclerotic coronary heart disease include hypertension, diabetes mellitus, family history, male gender, cigarette smoke and serum cholesterol. A total cholesterol level in excess of 225–250 mg/dl is associated with significant elevation of risk of CHD.

Cholesteryl esters are a major component of atherosclerotic lesions and the major storage form of cholesterol in arterial wall cells. Formation of cholesteryl esters is also a key step in the intestinal absorption of dietary cholesterol. Thus, inhibition of cholesteryl ester formation and reduction of serum cholesterol is likely to inhibit the progression of atherosclerotic lesion formation, decrease the accumulation of cholesteryl esters in the arterial wall, and block the intestinal absorption of dietary cholesterol.

A few azetidinones have been reported as being useful in lowering cholesterol and/or in inhibiting the formation of cholesterol-containing lesions in mammalian arterial walls. U.S. Pat. No. 4,983,597 discloses N-sulfonyl-2-azetidinones as anticholesterolemic agents and Ram, et al., in *Indian J. Chem., Sect. B.* 29B, 12 (1990), p. 1134–7, disclose ethyl 4-(2-oxoazetidin-4-yl)phenxy-alkanoates as hypolipidemic agents. European Patent Publication 264,231 discloses 1-substituted-4-phenyl-3-(2-oxo-alkylidene)-2-azetidinones as blood platelet aggregation inhibitors. European Patent 199,630 and European Patent Application 337,549 disclose elastase inhibitory substituted azetidinones said to be useful in treating inflammatory conditions resulting in tissue destruction which are associated with various disease states, e.g. atherosclerosis.

W093/02048, published Feb. 4, 1993, discloses substituted β-lactams useful as hypocholesterolemic agents.

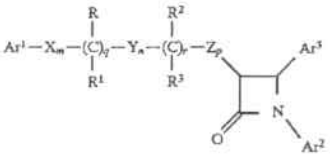
The regulation of whole-body cholesterol homeostasis in humans and animals involves the regulation of dietary cholesterol and modulation of cholesterol biosynthesis, bile acid biosynthesis and the catabolism of the cholesterol-containing plasma lipoproteins. The liver is the major organ responsible for cholesterol biosynthesis and catabolism and for this reason, it is a prime determinant of plasma cholesterol levels. The liver is the site of synthesis and secretion of very low density lipoproteins (VLDL) which are subsequently metabolized to low density lipoproteins (LDL) in the circulation. LDL are the predominant cholesterol-carrying lipoproteins in the plasma and an increase in their concentration is correlated with increased atherosclerosis.

When intestinal cholesterol absorption is reduced, by whatever means, less cholesterol is delivered to the liver. The consequence of this action is decreased hepatic lipoprotein (VLDL) production and an increase in the hepatic clearance of plasma cholesterol, mostly as LDL. Thus, the net effect of inhibiting intestinal cholesterol absorption is a decrease in plasma cholesterol levels.

The inhibition of cholesterol biosynthesis by 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase (EC1.1.1.34) inhibitors has been shown to be an effective way to reduce plasma cholesterol (Witzum, *Circulation*, 80, 5 (1989), p. 1101–1114) and reduce atherosclerosis. Combination therapy of an HMG CoA reductase inhibitor and a bile acid sequestrant has been demonstrated to be more effective in human hyperlipidemic patients than either agent in monotherapy (Illingworth, *Drugs*, 36 (Suppl. 3) (1988), p. 63–71).

SUMMARY OF THE INVENTION

Novel hypocholesterolemic compounds of the present invention are represented by the formula I



I

or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 and Ar^2 are independently selected from the group consisting of aryl and R^4-substituted aryl;

Ar^3 is aryl or R^5-substituted aryl;

X, Y and Z are independently selected from the group consisting of —CH_2—, —CH(lower alkyl)— and —C(dilower alkyl)—;

R and R^2 are independently selected from the group consisting of —OR^6, —$O(CO)R^6$, —$O(CO)OR^9$ and —$O(CO)NR^6R^7$;

R^1 and R^3 are independently selected from the group consisting of hydrogen, lower alkyl and aryl;

q is O or 1; r is O or 1; m, n and p are independently 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1, 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5;

R^4 is 1–5 substituents independently selected from the group consisting of lower alkyl, —OR^6, —$O(CO)R^6$, —$O(CO)OR^9$, —$O(CH_2)_{1-5}OR^6$, —$O(CO)NR^6R^7$, —NR^6R^7, —$NR^6(CO)R^7$, —$NR^6(CO)OR^9$, —$NR^6(CO)NR^7R^8$, —$NR^6SO_2R^9$, —$COOR^6$, —$CONR^6R^7$, —COR^6, —$SO_2NR^6R^7$, $S(O)_{0-2}R^9$, —$O(CH_2)_{1-10}$—$COOR^6$, —$O(CH_2)_{1-10}CONR^6R^7$, —(lower alkylene)$COOR^6$, —CH=CH—$COOR^6$, —CF_3, —CN, —NO_2 and halogen;

R^5 is is 1–5 substituents independently selected from the group consisting of —OR^6, —$O(CO)R^6$, —$O(CO)OR^9$, —$O(CH_2)_{1-5}OR^6$, —$O(CO)NR^6R^7$, —NR^6R^7, —$NR^6(CO)R^7$, —$NR^6(CO)OR^9$, —$NR^6(CO)NR^7R^8$, —$NR^6SO_2R^9$, —$COOR^6$, —$CONR^6R^7$, —COR^6, —$SO_2NR^6R^7$, $S(O)_{0-2}R^9$, —$O(CH_2)_{1-10}$—$COOR^6$, —$O(CH_2)_{1-10}CONR^6R^7$, —(lower alkylene)$COOR^6$ and —CH=CH—$COOR^6$;

R^6, R^7 and R^8 are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

R^9 is lower alkyl, aryl or aryl-substituted lower alkyl.

R^4 is preferably 1–3 independently selected substituents, and R^5 is preferably 1–3 independently selected substituents. Preferred are compounds of formula I wherein Ar^1 is phenyl or R^4-substituted phenyl, especially (4-R^4)-substituted phenyl. Ar^2 is preferably phenyl or R^4-substituted phenyl, especially (4-R^4)-substituted phenyl. Ar^3 is preferably R^5-substituted phenyl, especially (4-R^5)-substituted phenyl. When Ar^1 is (4-R^4)-substituted phenyl, R^4 is preferably a halogen. When Ar^2 and Ar^3 are R^4- and R^5-substituted phenyl, respectively, R^4 is preferably halogen or —OR^6 and R^5 is preferably —OR^6, wherein R^6 is lower alkyl or hydrogen. Especially preferred are compounds wherein each of Ar^1 and Ar^2 is 4-fluorophenyl and Ar^3 is 4-hydroxyphenyl or 4-methoxyphenyl.

X, Y and Z are each preferably —CH_2—. R^1 and R^3 are each preferably hydrogen. R and R^2 are preferably —OR^6 wherein R^6 is hydrogen, or a group readily metabolizable to a hydroxyl (such as —O(CO)R^6, —O(CO)OR^9 and —O(CO)NR^6R^7, defined above).

The sum of m, n, p, q and r is preferably 2, 3 or 4, more preferably 3. Preferred are compounds wherein m, n and r are each zero, q is 1 and p is 2. Also preferred are compounds wherein p, q and n are each zero, r is 1 and m is 2 or 3. More preferred are compounds wherein m, n and r are each zero, q is 1, p is 2, Z is —CH_2— and R is —OR^6, especially when R^6 is hydrogen. Also more preferred are compounds wherein p, q and n are each zero, r is 1, m is 2, X is —CH_2— and R^2 is —OR^6, especially when R^6 is hydrogen.

Another group of preferred compounds is that wherein Ar^1 is phenyl or R^4-substituted phenyl, Ar^2 is phenyl or R^4-substituted phenyl and Ar^3 is R^5-substituted phenyl. Also preferred are compounds wherein Ar^1 is phenyl or R^4-substituted phenyl, Ar^2 is phenyl or R^4-substituted phenyl, Ar^3 is R^5-substituted phenyl, and the sum of m, n, p, q and r is 2, 3 or 4, more especially 3. More preferred are compounds wherein Ar^1 is phenyl or R^4-substituted phenyl, Ar^2 is phenyl or R^4-substituted phenyl, Ar^3 is R^5-substituted phenyl, and wherein m, n and r are each zero, q is 1 and p is 2, or wherein p, q and n are each zero, r is 1 and m is 2 or 3.

This invention also relates to a method of lowering the serum cholesterol level in a mammal in need of such treatment comprising administering an effective amount of a compound of formula I. That is, the use of a compound of the present invention as an hypocholesterolemic agent is also claimed.

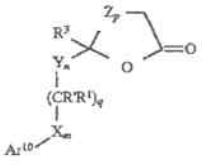
In still another aspect, the present invention relates to a pharmaceutical composition comprising a serum cholesterol-lowering effective amount of a compound of formula I in a pharmaceutically acceptable carrier.

The present invention also relates to a method of reducing plasma cholesterol levels, and to a method of treating or preventing atherosclerosis, comprising administering to a mammal in need of such treatment an effective amount of a combination of a hydroxy-substituted azetidinone cholesterol absorption inhibitor of formula I and a cholesterol biosynthesis inhibitor. That is, the present invention relates to the use of a hydroxy-substituted azetidinone cholesterol absorption inhibitor of formula I for combined use with a cholesterol biosynthesis inhibitor (and, similarly, use of a cholesterol biosynthesis inhibitor for combined use with a hydroxy-substituted azetidinone cholesterol absorption inhibitor of formula I) to treat or prevent atherosclerosis or to reduce plasma cholesterol levels.

In yet another aspect, the invention relates to a pharmaceutical composition comprising an effective amount of a hydroxy-substituted azetidinone cholesterol absorption inhibitor of formula I, a cholesterol biosynthesis inhibitor, and a pharmaceutically acceptable carrier. In a final aspect, the invention relates to a kit comprising in one container an effective amount of a hydroxy-substituted azetidinone cholesterol absorption inhibitor of formula I in a pharmaceutically acceptable carrier, and in a separate container, an effective amount of a cholesterol biosynthesis inhibitor in a pharmaceutically acceptable carrier.

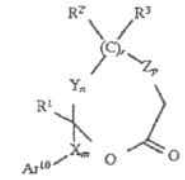
In yet another aspect, the invention relates to a process for preparing certain compounds of formula I comprising the steps:

(a) treating with a strong base a lactone of the formula



A

or



B

wherein R' and $R^{2'}$ are R and R^2, respectively, or are suitably protected hydroxy groups; Ar^{10} is Ar^1, a suitably protected hydroxy-substituted aryl or a suitably protected amino-substituted aryl; and the remaining variables are as defined above, provided that in lactone of formula B, when n and r are each zero, p is 1–4;

(b) reacting the product of step (a) with an imine of the formula

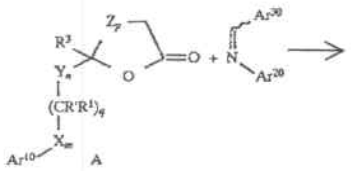
wherein Ar^{20} is Ar^2, a suitably protected hydroxy-substituted aryl or a suitably protected amino-substituted aryl; and Ar^{30} is Ar^3, a suitably protected hydroxy-substituted aryl or a suitably protected amino-substituted aryl;

c) quenching the reaction with an acid;

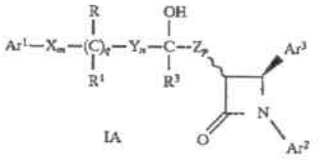
d) optionally removing the protecting groups from R', $R^{2'}$, Ar^{10}, Ar^{20} and Ar^{30}, when present; and

e) optionally functionalizing hydroxy or amino substituents at R, R^2, Ar^1, Ar^2 and Ar^3.

Using the lactones shown above, compounds of formula IA and IB are obtained as follows:

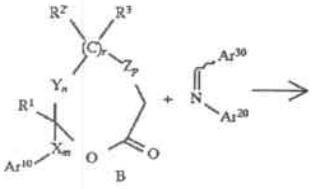


A

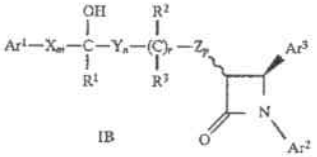


IA

wherein the variables are as defined above.



B



IB

wherein the variables are as defined above.

DETAILED DESCRIPTION

As used herein, the term "lower alkyl" means straight or branched alkyl chains of 1 to 6 carbon atoms.

"Aryl" means phenyl, naphthyl, indenyl, tetrahydronaphthyl or indanyl.

"Halogeno" refers to fluorine, chlorine, bromine or iodine atoms.

The above statement, wherein R^6, R^7 and R^8 are said to be independently selected from a group of substituents, means that R^6, R^7 and R^8 are independently selected, but also that where an R^6, R^7 or R^8 variable occurs more than once in a molecule, those occurrences are independently selected (e.g., if R is $—OR^5$ wherein R^5 is hydrogen, R^4 can be $—OR^6$ wherein R^5 is lower alkyl).

Compounds of the invention have at least one asymmetric—carbon atom and therefore all isomers, including enantiomers and diastereomers are contemplated as being part of this invention. The invention includes d and l isomers in both pure form and in admixture, including racemic mixtures. Isomers can be prepared using conventional techniques, either by reacting chiral starting materials or by separating isomers of a compound of formula I. Isomers may also include geometric isomers, e.g. when a double bond is present. All such geometric isomers are contemplated for this invention.

Those skilled in the art will appreciate that for some compounds of formula I, one isomer will show greater pharmacological activity than another isomer.

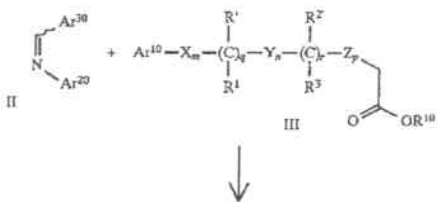
Compounds of the invention with an amino group can form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salt is prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt. The free base form may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium bicarbonate. The free base form differs from its respective salt form somewhat in certain physical properties, such as solubility in polar solvents, but the salt is otherwise equivalent to its respective free base form for purposes of the invention.

Certain compounds of the invention are acidic (e.g., those compounds which possess a carboxyl group). These compounds form pharmaceutically acceptable salts with inorganic and organic bases. Examples of such salts are the sodium, potassium, calcium, aluminum, gold and silver salts. Also included are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

Cholesterol biosynthesis inhibitors for use in the combination of the present invention include HMG CoA reductase inhibitors such as lovastatin, pravastatin, fluvastatin, simvastatin, and Cl-981; HMG CoA synthetase inhibitors, for example L-659,699 ((E,E)-11-[3'R-(hydroxy-methyl)-4'-oxo-2'R-oxetanyl]-3,5,7R-trimethyl-2,4-undecadienoic acid); squalene synthesis inhibitors, for example squalestatin 1; and squalene epoxidase inhibitors, for example, NB-598 ((E)-N-ethyl-N-(6,6-dimethyl-2-hepten-4-ynyl)-3-[(3,3'-bithiophen-5-yl)methoxy]benzene-methanamine hydrochloride) and other cholesterol biosynthesis inhibitors such as DMP-565. Preferred HMG CoA reductase inhibitors are lovastatin, pravastatin and simvastatin.

Compounds of formula I can be prepared by known methods, for example those described below and in W093/02048.

Method A:



II

III

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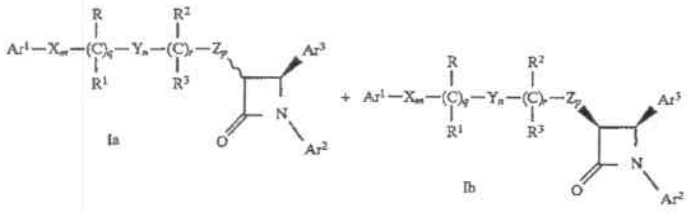
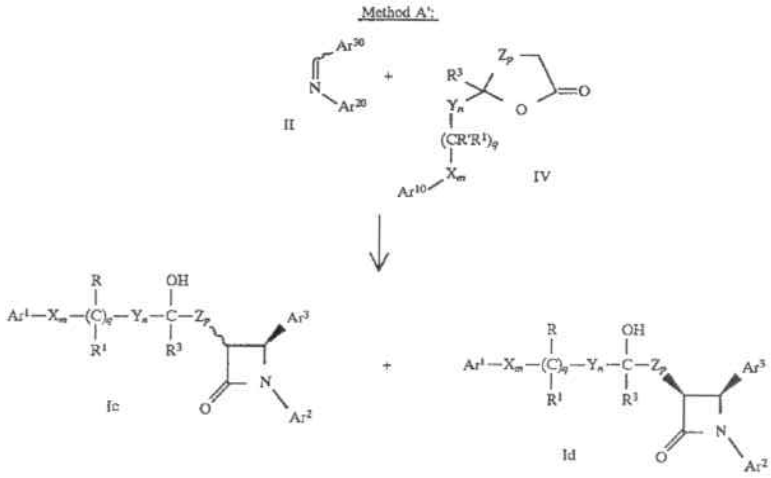
Method A:



Compounds of formula Ia and Ib, wherein Ar^1, Ar^2, Ar^3, X, Y, Z, R, R^1, R^2, R^3, m, n, p, q and r are as defined above, can be prepared by treatment of an ester of formula III, wherein known in the art. Aldehydes of formula Ar^{30}—CHO and amines of formula Ar^{20}—NH_2 are commercially available or can be prepared via known procedures.

Method A':



R^{10} is lower alkyl such as ethyl or a chiral moiety such as menthyl or 10-(diisopropylsulfonamido)isobornyl, and the remaining variables are as defined above with a strong base such as lithium diisopropylamide (LDA) in a suitable solvent such as tetrahydrofuran (THF) at −78° C. A solubilizing agent such as hexamethylphosphoric triamide (HMPA) may optionally be added as a cosolvent. An imine of formula II, wherein Ar^{20} and Ar^{30} are as defined above, is added, the reaction mixture is either warmed to room temperature or maintained at a suitable low temperature such as −78° C. for the appropriate time, followed by quenching with a suitable acid such as 1N HCl. The product is isolated using conventional purification techniques. When a protecting group as defined in Table 1 (below) is present on one or more of the optionally protected groups, an additional step comprising removal of the protecting group by conventional techniques is needed. However, for compounds of formula Ia, Ib, or any compound of formula I wherein a protected hydroxy group Ar^{10}, Ar^{20}, Ar^{30}, R' or R'' is an alkoxy or benzyloxy group, such a protecting group need not be removed to obtain a compound of formula I. When a chiral ester of formula III is used, the resulting compound of formula Ia or Ib is not racemic.

Imines of formula II (Ar^{30}—CH═N—Ar^{20}) can be prepared from aldehydes of the formula Ar^{30}—CHO and amines of the formula Ar^{20}—NH_2 by procedures well

Compounds of formula Ic and Id, wherein the variables are as defined above, can be prepared by a process comprising the following steps:

(a) Treat a lactone of formula IV, wherein the variables are as defined above, with a strong base such as an alkyllithium (e.g., n-butyllithium), a metal hydride (e.g., sodium hydride), a metal alkoxide (e.g., sodium methoxide), a metal halide (e.g., $TiCl_4$), metal exchange of the lithium enolate with a metal halide (e.g., zinc chloride), metal exchange of the lithium enolate with a metal alkyl (e.g., 9-borabicyclononyl triflate), or, preferably, a metalamide (e.g., LDA), in a suitable anhydrous organic solvent such as dry THF, ether or benzene, in a dry, inert atmosphere, e.g., under nitrogen. The reaction is carried out at about 0° C. to about −85° C., preferably about −78° C., over a period of about 5 to about 60 minutes, preferably about 30 minutes. 1–50% of solubilizing cosolvents may optionally be added, preferably about 10% HMPA.

(b) Add an imine of formula II, wherein Ar^{20} and Ar^{30} are as defined above, to the product of step (a) over a period of 5 to 60 minutes, preferably 30 minutes, maintaining the reaction mixture at about 0° C. to about −85° C., preferably about −78° C., for 1 to 12 hours, preferably about 3 hours, or warming the reaction mixture over that time period at a rate of about 10° C. per hour to

about 70° C. per hour, preferably about 30° C. per hour, to a temperature of about 20° C.

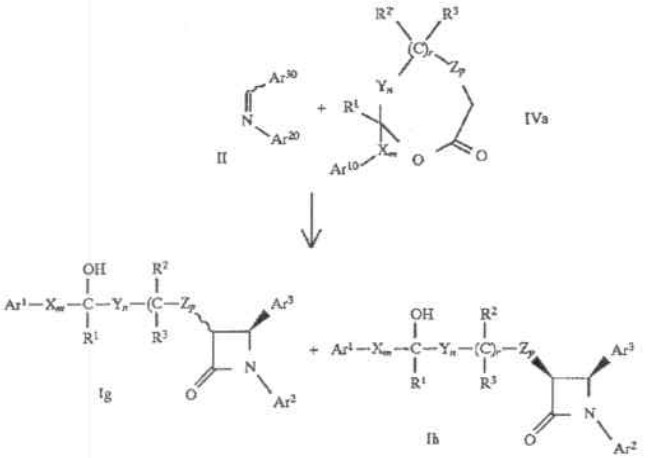
(c) Quench the reaction with a suitable acid such as HCl (1N).

(d) The protecting groups on R', $R^{2'}$, Ar^{10}, Ar^{20} and Ar^{30}, when present, are removed, if desired, by methods well known in the art, for example silyl protecting groups are removed by treatment with fluoride.

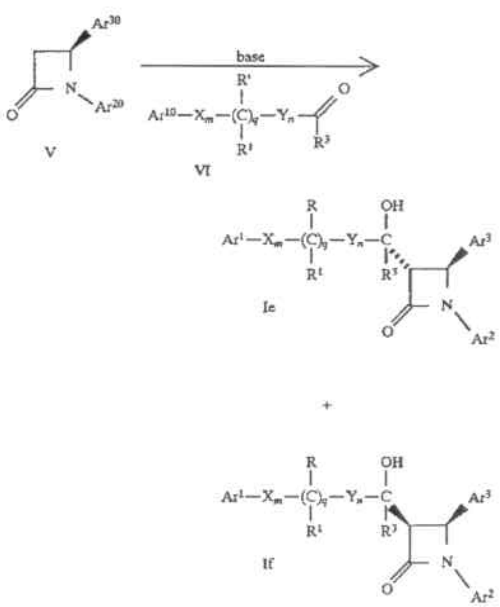
e) Compounds of formula I wherein any of R and R^2, when present, are OR^6 wherein R^6 is hydrogen, can be converted by well known methods to other compounds of formula I wherein R and R^2 are functionalized, i.e., are independently selected from the group consisting of OR^{6a}, —O(CO)R^6, —O(CO)OR^9 and —O(CO)NR^6R^7, wherein R^6, R^7 and R^9 are as defined above and R^{6a} is lower alkyl, aryl, or aryl-lower alkyl. For example, treatment of the alcohol with an alkyl halide in the presence of a suitable base such as NaH will afford alkoxy-substituted compounds (i.e., R or R^2 is OR^6, wherein R^6 is lower alkyl); treatment of the alcohol with an acylating agent such as acetylchloride will result in compounds wherein R or R^2 is —OC(O)R^6; treatment of the alcohol with phosgene followed by an alcohol of the formula HOR^9 affords compounds substituted with a —OC(O)OR^9 group; and treatment of the alcohol with phosgene followed by an amine of the formula HNR^6R^7 affords compounds wherein R or R^2 is —OC(O)NR^6R^7. Compounds of formula I wherein any of Ar^1, Ar^2 or Ar^3 has a hydroxy or amino group can be similarly functionalized to obtain other compounds of formula I, i.e., wherein R^4 and R^5 are independently —OR^{6a}, —O(CO)R^6, —O(CO)OR^9, —$O(CH_2)_{1-5}OR^6$, —O(CO)NR^6R^7, —NR^6R^7, —NR^6(CO)R^7, —NR^6(CO)OR^9, —NR^6(CO)NR^7R^8 or —$NR^6SO_2R^9$.

The product of step c, d or e is isolated using conventional purification techniques such as extraction, crystallization or, preferably, silica gel 60 chromatography. When a chiral lactone is used, the resulting compound of formula Ic or Id is not racemic.

Using the procedure described in steps (a)–(e), lactones of formula IVa can be used to prepare compounds of formula Ig and Ih, provided that when n and r are each zero, p is 1–4:



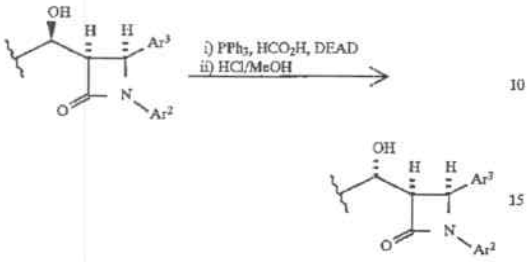
Lactones of formulae IV and IVa are known in the art or can be prepared by methods well known in the art. See, for example, U.S. Pat. No. 4,375,475 and *J. Agric. Food Chem.*, 30 (5) (1982) p. 920–4.



Azetidinones of formula V, wherein Ar^{20} and Ar^{30} are as defined above, can be reacted to form compounds of formula Ie and If (i.e., compounds of formula I wherein r is 1, R^2 is hydroxy, and p is zero) by treatment of azetidinone V with a strong base such as lithium isopropylcyclohexylamide in a suitable solvent such as THF in the presence or absence of HMPA at −78° C., followed by the addition of an aldehyde or ketone of VI, wherein Ar^{10}, X, Y, R', R^1, R^3, m, n and q are as defined above. As in the case of Method A, protecting groups at Ar^{10}, Ar^{20}, Ar^{30}, R' and $R^{2'}$ are removed as necessary.

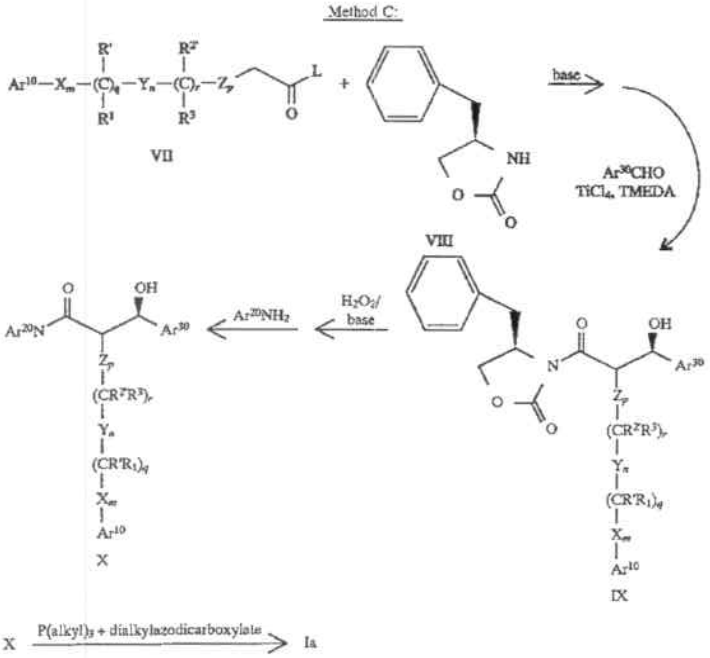
This process provides several of the possible diastereomers which can be separated by a combination of

crystallization, silica gel chromatography and HPLC, using techniques well known in the art. The remaining diastereomers can be obtained by inversion reactions such as the Mitsunobu reaction sequence outlined below, wherein partial structures of formula If are shown:



In the above known process, DEAD is diethylazodicarboxylate and PPh_3 is triphenylphosphine. The reactants are stirred at room temperature overnight and the resultant formate ester is converted to the corresponding hydroxy compound with the desired stereochemistry.

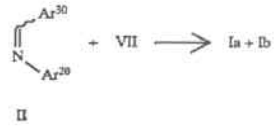
Method C:



X $\xrightarrow{P(alkyl)_3 + dialkylazodicarboxylate}$ Ia

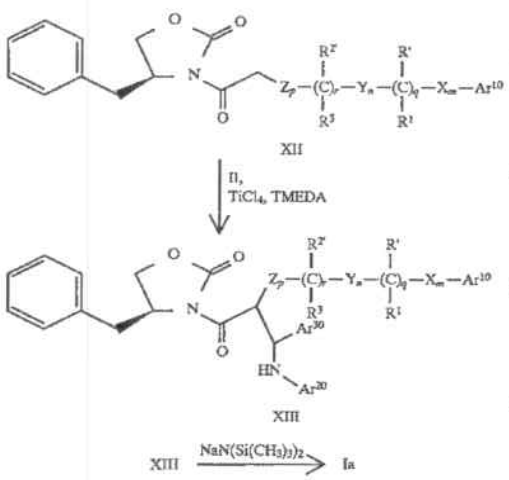
Compounds of formula Ia as defined above can be prepared by reacting a chiral auxiliary such as the compound of formula VIII with an activated carboxylic acid derivative of formula VII, for example an acid chloride (L=Cl), a mixed anhydride formed with phenyl phosphorodichloridate (L=OP(O)(Cl)OPh), an N-methyl-pyridinium ester formed from the reaction of an acid with N-methyl-2-chloropyridinium iodide (L=2-oxy-N-methylpyridinium iodide), and a 2-thiopyridyl ester formed from the reaction of an acid chloride and 2-thiopyridine, wherein the remaining variables are as defined above; enolizing the resultant product, for example with $TiCl_4$ and tetramethylethylenediamine (TMEDA); condensing with an aldehyde, $Ar^{30}CHO$; hydrolyzing to the corresponding acid, then reacting the compound of formula IX with an amine, $Ar^{20}NH_2$; and cyclizing the resultant compound of formula X, with, for example a trialkylphosphine and a dialkylazodicarboxylate. As in the case of Method A, protecting groups at Ar^{10}, Ar^{20}, Ar^{30}, R' and R2' are removed as necessary. This procedure is described in detail in W093/02048.

Method D:



Compounds of formula Ia as defined above can also be prepared by treatment of an imine of formula II, wherein Ar^{20} and Ar^{30} are as defined above, with an activated carboxylic acid derivative of formula VII as defined above in the presence of a tertiary amine base such as triethylamine, tributylamine or diethylisopropylamine in an inert solvent such as CH_2Cl_2. Again, as in the case of Method A, protecting groups at Ar^{10}, Ar^{20}, Ar^{30}, R' and R2' are removed as necessary. Use of other bases, e.g., pyridine, favors formation of compounds of formula Ib.

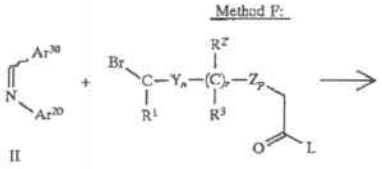
Method E:



In the first step, compound XII is dissolved in a suitable solvent, e.g., anhydrous CH_2Cl_2, and treated with a Lewis acid, e.g., $TiCl_4$ at about −60° C. to 0° C., preferably at about −25° C., under a dry, inert atmosphere, e.g., argon. A tertiary amine base such as TMEDA is added and the mixture stirred at about −60° C. to 0° C., preferably at about −25° C. to −15° C., for a period of about 1 h. An imine of formula $Ar^{30}CH{=}NAr^{20}$ is added neat or optionally as a solution in a suitable solvent, e.g. anhydrous CH_2Cl_2, over a period of about 5 min, and the reaction is stirred vigorously at about −60° C. to 0° C., preferably at about −25° C. to −15° C., for about 3 to 6 h, preferably about 4 h or until the reaction is complete by TLC. An acid, e.g. acetic acid, is added to reaction at the reaction temperature and the mixture is allowed to warm to room temperature slowly with stirring for about 1–3 hours, preferably about 2 hours. The compound of formula XIII is isolated by extraction with a suitable solvent, e.g. CH_2Cl_2, then purified by crystallization or silica gel chromatography.

In the second step, the product is treated with a strong non-nucleophilic base, such as sodium or lithium bistrimethylsilylamide at about −78° C. to 10° C. After reaction, the mixture is poured into aqueous tartaric acid and the product isolated from the organic layer. As in the case of Method A, protecting groups at Ar^{10}, Ar^{20}, Ar^{30}, R' and $R^{2'}$ are removed as necessary, This process, including the preparation of the starting material of formula XII, is also described in greater detail in W093/02048.

Method F:



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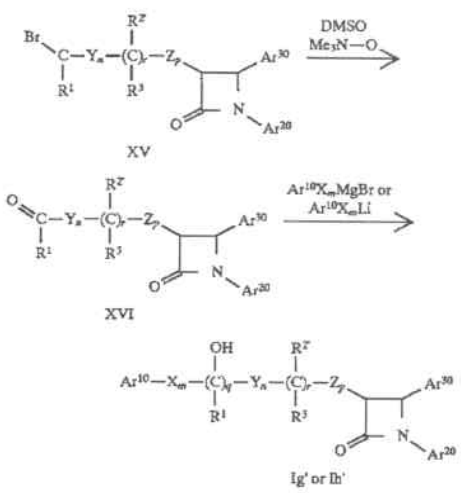
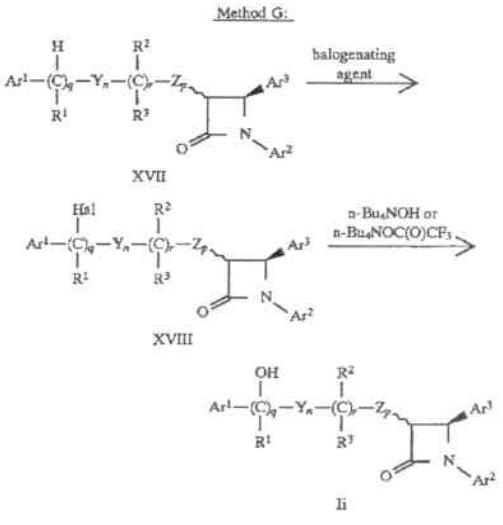
Method F:



Compounds of formula Ig' and Ih' (i.e., compounds of formula I wherein R is OH), wherein $R^{2'}$ is a protected hydroxy group as defined above, and the remaining variables are as defined above, can be prepared by reacting an imine of formula II and a carboxylic acid derivative of formula XIV, wherein the variables are as defined above, according to Method D, followed by oxidation of the resultant halide of formula XV by treatment with an oxidizing agent such as trimethylamine oxide, CrO_3 or ozone in a solvent such as DMSO. The resultant aldehyde or ketone of formula XVI is then reacted with an aryl organometallic reagent (e.g., $Ar^{10}X_mMgBr$, $Ar^{10}X_mLi$, $Ar^{10}X_mMgCl$ or $Ar^{10}X_mCeCl_2$) to obtain a compound of formula Ig' or Ih'. As described above, the Ar^{10}, Ar^{20}, Ar^{30} and $R^{2'}$ substituents can be converted to the desired Ar^1, Ar^2, Ar^3 and R^2 substituents by procedures well known in the art.

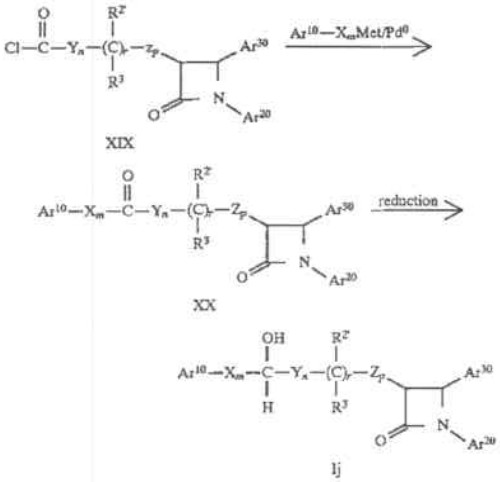
Method G:



Compounds of formula II having a hydroxy substituent on the side chain adjacent to the Ar^1 group (i.e., compounds of

formula I wherein m is 0) can be prepared by heating a compound of formula XVII, prepared by Method D, above, wherein the variables are as defined above, for about 1–6 hours at about 60° C. to 100° C. with a halogenating agent such as N-bromosuccinimide (NBS) in a suitable solvent such as CCl_4 in the presence of an initiating agent such as benzoyl peroxide. The resultant compound of formula XVIII, wherein Hal is Cl, Br or I and the remaining variables are as defined above, is then heated in a suitable solvent such as CH_2Cl_2 with a tetraalkyl-ammonium salt such as tetra n-butyl-ammonium hydroxide (n-Bu_4NOH) to obtain the compound of formula Ii. Alternatively, compound XVIII can be heated in a suitable solvent such as CH_2Cl_2 with tetra n-butylammonium trifluoroacetate (n-$Bu_4NOC(O)CF_3$) followed by treatment with a mild base such as ethanol saturated with NH_3 to obtain compound Ii.

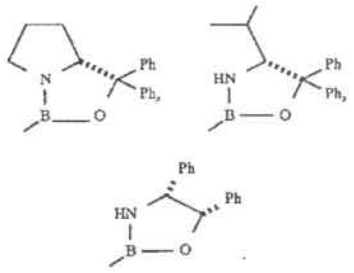
Method H:



Compounds of formula Ij (i.e., compounds of formula I wherein R is OH, R^1 is H and q is 1) are prepared from compound XIX in 2 steps. First, a compound of formula XIX, wherein the variables are as defined above, is dissolved in a suitable anhydrous solvent, e.g. THF, at about –20° C. to about 22° C., preferably at about 0° C. under a dry inert atmosphere, e.g. argon and adding a transition metal source, e.g. tetrakis(triphenylphosphine)-palladium or palladium acetate/triphenyl phosphine. An organometallic of formula $Ar^{10}—X_m—Met$, wherein Ar^{10}, X and m are as defined above and Met is, for example, ZnCl or $B(OH)_2$, is added to the reaction mixture at about –20° C. to about 22° C., preferably at about 0° C., the reaction mixture is stirred for about 15 min to 4 h, preferably about 1 h, and is then allowed to warm to about 22° C. Addition of dilute acid, e.g. 1N HCl, followed by extraction with a suitable organic solvent, e.g. ethyl acetate (EtOAc), produces compound XX.

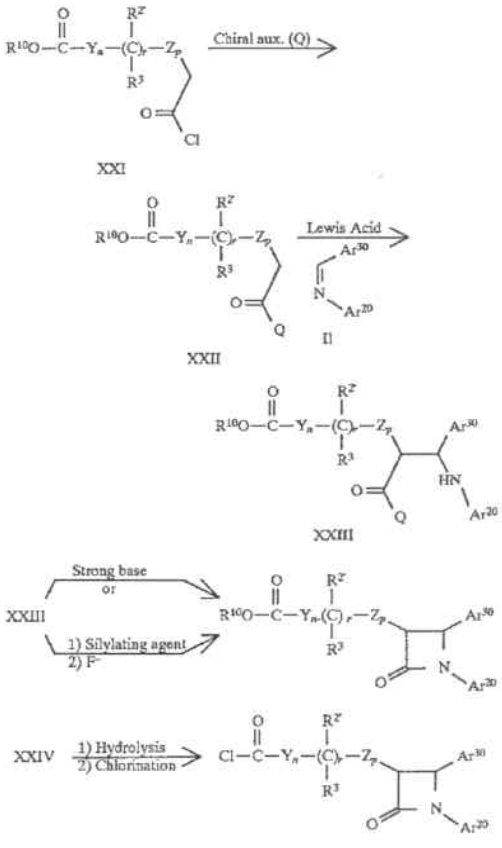
The ketone of formula XX is dissolved in a suitable solvent, e.g. CH_3OH, a hydrogenation catalyst is added, e.g. Pd on carbon, and the mixture is exposed to H_2 gas under a pressure of about 14 psi to 100 psi, preferably about 60 psi for about 1 to 24 h, preferably about 16 h. The hydrogenation catalyst is removed by filtration and the solvent is removed in vacuo to produce a compound Ij as a mixture of alcohol diastereomers which can be separated by conventional means.

Alternatively, a ketone of formula XX is dissolved in a suitable solvent, e.g. THF, at about –40° C. to about 22° C., preferably at about 0° C., and a suitable reducing agent such as $NaBH_4$, a substituted borohydride (e.g., [cbz-proline]$_3$BHNa) or a borane is added, optionally in the presence of a suitable chiral promotor present either in catalytic or stoichiometric amounts, e.g., chiral borane of structures:



Addition of dilute acid, e.g., 1N HCl, followed by extraction with a suitable solvent produces compounds of formula Ij. As above, protecting groups at Ar^{10}, Ar^{20}, Ar^{30} and $R^{2'}$ are removed as necessary. When either a chiral reagent or a chiral promotor is used, the resulting product is non-racemic.

Compounds of formula XIX can be prepared by a multi-step procedure as represented below:



Compounds of formula XXI, wherein R^{10} is lower alkyl and the remaining variables are as defined above, are commer-

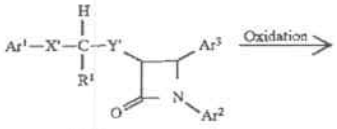
cially available or can be prepared by treating the corresponding carboxylic acid (i.e., compounds wherein the Cl is replaced by a hydroxy group) with a chlorinating agent, e.g. $SOCl_2$ or oxalyl chloride, under a dry atmosphere, neat or in a suitable inert organic solvent, e.g. toluene at about 40° C. to 110° C., preferably about 70° C.; alternatively, a catalyst made be added, e.g. dimethylformamide (DMF), the reaction is conducted at about 22° C. and the solvent and excess reagents are removed in vacuo. The compound XXI is reacted with a chiral auxiliary such as (S)-4-phenyl-2-oxazolidinone according to the following procedure: a chiral auxiliary is treated with a strong base such as an alkyllithium, a metal hydride or a tertiary amine base such as triethylamine, in a suitable anhydrous organic solvent, e.g., dry THF, under a dry, inert atmosphere, e.g. argon, at about −85° C. to 22° C., preferably about 0° C., for about 10 min to 60 min, preferably about 30 minutes. The resulting anion is reacted, without isolation, with compound XXI in a suitable anhydrous organic solvent, e.g. dry THF, under a dry, inert atmosphere, e.g. argon, at about −85° C. to about 22° C., preferably 0° C., for about 30 min to 60 min, preferably 30 min. The reaction is warmed to about 22° C. and continued for 1 to 12 h, preferably 6 h. water is added and compound XXII is isolated by extraction and purified by crystallization.

The compound of formula XXII is treated in the same manner as described in step 1 of Method E to obtain a compound XXIII.

Azetidinone ring closure can be accomplished by alternative procedures. By one method, a compound of formula XXIII is treated with a strong non-nucleophilic base, such as sodium or lithium-bistrimethylsilylamide, in a suitable inert organic solvent, e.g. CH_2Cl_2, at about −78° C. to about 10° C., preferably about 0° C. The mixture is stirred for about 1 to 2 hours while gradually warming to about 22° C. Compound XXIV is isolated by conventional extraction with CH_2Cl_2. In another, two-step method, a compound of formula XXIII is first treated with mild silylating agent, e.g. N,O-bis(trimethylsilyl)acetamide at about 0° C. to about 100° C., preferably about 40° C. for about 10 min to 60 min, preferably 30 min, then treated with a fluoride anion source, e.g. tetrabutylammonium fluoride (TBAF), at about 0° C. to about 100° C., preferably 40° C., and allowed to stir for about 0.5 to about 4 hours, preferably about 2 hours. Compound XXIV is isolated by conventional extraction methods.

The compound of formula XXIV is hydrolysed by a suitable base, e.g. LiOH, in a suitable solvent, e.g. 66% CH_3OH/water at about 0° C. to about 50° C., preferably 22° C., for about 1 to 4 hours, preferably 2 hours, then extracted with a suitable solvent, e.g. EtOAc. The resulting acid is converted to the acid chloride as described above by treatment with a chlorination agent, e.g. oxalyl chloride, to afford compound XIX.

Method I:



XXV

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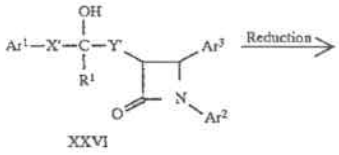
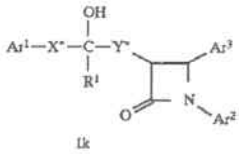
Method I:



XXVI



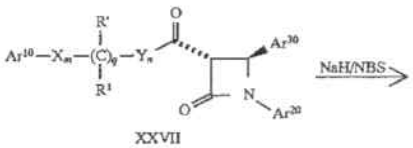
Ik

Compounds of formula Ik, wherein Ar^1, Ar^2, Ar^3 and R^1 are as defined above, one of X" and Y" is $—CH_2CH_2—$ and the other is selected from the group consisting of $—CH_2CH_2—$, $—CH_2—$, —CH(lower alkyl)—, —CH(dilower alkyl) and a bond, are prepared by oxidation of an alkene of formula XXV, wherein one of X' and Y' is —CH=CH— and the other is —CH=CH—, $—CH_2$, $—CH_2CH_2—$, —CH(lower alkyl)—, —CH(dilower alkyl) or a bond, and the remaining variables are as defined above, can be prepared by the following two step procedure.

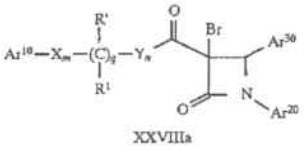
A compound of formula XXV, which can be prepared by Method D, above, is treated with an oxidizing agent such as SeO_2, phenylselenic anhydride or CrO_3 in a suitable solvent such as dioxane at about 22° to 100° C. for about 0.5 to 12 hours. After the starting material is consumed as determined by TLC, or 12 hours, the reaction is cooled to about 22° C. and the product XXVI is isolated by extraction.

In the second step, an allylic alcohol of formula XXVI is dissolved in a suitable solvent, e.g., EtOAc, a hydrogenation catalyst is added, e.g., Pd on carbon, and the mixture is exposed to H_2 gas under a pressure of about 14 psi to 60 psi for about 1 to 12 hours. The hydrogenation catalyst is removed in vacuo to obtain a compound of formula Ik.

Method J:

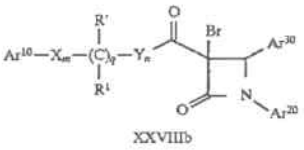


XXVII



XXVIIIa

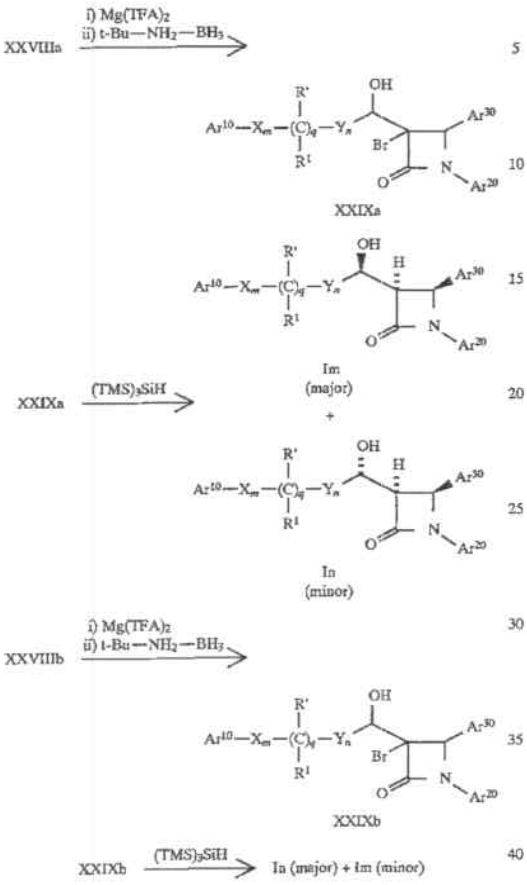
+



XXVIIIb

-continued

Method J:



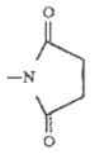
Alcohols of formula Im and In (i.e., compounds of formula I wherein r is 1, R^2 is —OH, R^3 is hydrogen and p is 0) can be selectively obtained from ketones of formula XXVII in three steps comprising bromination, reduction and debromination. Since the stereochemistry of the major isomers of alcohols XXIXa and XXIXb are different, one can selectively prepare either diastereomeric alcohol.

In the above process, a ketone of formula XXVII, which can be prepared by oxidation of the corresponding hydroxy compound by well known methods, is halogenated, for example by treatment in an inert solvent, e.g., THF, with NaH followed by N-bromosuccinimide, to obtain a mixture of 3-bromo-ketone compounds XXVIII (a and b). Compounds XXVIIIa and XXVIIIb are then separately reduced to the corresponding alcohols, for example by treatment with magnesium trifluoroacetate ($Mg(TFA)_2$) and t-butylamine borane (t-Bu-NH_2-BH_3) in an inert solvent such as THF at a temperature of about −78° C. to 0° C. The resultant alcohols XXIX are dehalogenated by treatment with tris(trimethylsilyl) silane ($(TMS)_3SiH$) in a solvent such as toluene in the presence of a radical initiator such as 2,2'-azobisisobutyronitrile (AIBN) to obtain a mixture of isomers Im and In which can be separated into individual enantiomers by conventional means, e.g., HPLC. Again, protecting groups at Ar^{10}, Ar^{20}, Ar^{30} and R' are removed as necessary.

Starting compounds III, V, VI, VII, VIII, XIV, XVII, XXI and XXV are all either commercially available or well known in the art and can be prepared via known methods.

Reactive groups not involved in the above processes can be protected during the reactions with conventional protecting groups which can be removed by standard procedures after the reaction. The following Table 1 shows some typical protecting groups:

TABLE 1

Group to be Protected	Group to be Protected and Protecting Group
—COOH	—COOalkyl, —COObenzyl, —COOphenyl
>NH	>NCOalkyl, >NCObenzyl, >NCOphenyl
	>NCH2OCH2CH2Si(CH3)3 >NC(O)OC(CH3)3,
	>N-benzyl, >NSi(CH3)3, >NSi—C(CH3)3 (CH3 CH3)
—NH2	
—OH	—OCH3, —OCH2OCH3, —OSi—C(CH3)3 (CH3 CH3)
	—OSi(CH3)3, or —OCH2phenyl

We have found that the compounds of this invention lower serum lipid levels, in particular serum cholesterol levels. Compounds of this invention have been found to inhibit the intestinal absorption of cholesterol and to significantly reduce the formation of liver cholesteryl esters in animal models. Thus, compounds of this invention are hypocholesterolemic agents by virtue of their ability to inhibit the intestinal absorption and/or esterification of cholesterol; they are, therefore, useful in the treatment and prevention of atherosclerosis in mammals, in particular in humans.

The in vivo activity of the compounds of formula I can be determined by the following procedure:

In Vivo Assay of Hypolipidemic Agents Using the Hyperlipidemic Hamster

Hamsters are separated into groups of six and given a controlled cholesterol diet (Purina Chow #5001 containing 0.5% cholesterol) for seven days. Diet consumption is monitored to determine dietary cholesterol exposure in the face of test compounds. The animals are dosed with the test compound once daily beginning with the initiation of diet. Dosing is by oral gavage of 0.2 mL of corn oil alone (control group) or solution (or suspension) of test compound in corn oil. All animals moribund or in poor physical condition are euthanized. After seven days, the animals are anesthetized by intramuscular (IM) injection of ketamine and sacrificed by decapitation. Blood is collected into vacutainer tubes containing EDTA for plasma lipid analysis and the liver excised for tissue lipid analysis. Lipid analysis is conducted as per published procedures (Schnitzer-Polokoff, R., et al,

Comp. Biochem. Physiol, 99A, 4 (1991), p. 665–670) and data is reported as percent reduction of lipid versus control.

The present invention also relates to a pharmaceutical composition comprising a compound of formula I and a pharmaceutically acceptable carrier. The compounds of formula I can be administered in any conventional dosage form, preferably an oral dosage form such as a capsule, tablet, powder, cachet, suspension or solution. The formulations and pharmaceutical compositions can be prepared using conventional pharmaceutically acceptable excipients and additives and conventional techniques. Such pharmaceutically acceptable excipients and additives include non-toxic compatible fillers, binders, disintegrants, buffers, preservatives, anti-oxidants, lubricants, flavorings, thickeners, coloring agents, emulsifiers and the like.

The daily hypocholesteremic dose of a compound of formula I is about 0.1 to about 30 mg/kg of body weight per day, preferably about 0.1 to about 15 mg/kg. For an average body weight of 70 kg, the dosage level is therefore from about 5 mg to about 1000 mg of drug per day, given in a single dose or 2–4 divided doses . The exact dose, however, is determined by the attending clinician and is dependent on the potency of the compound administered, the age, weight, condition and response of the patient.

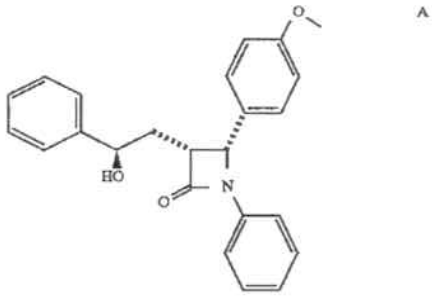
For the combinations of this invention wherein the hydroxy substituted azetidinone is administered in combination with a cholesterol biosynthesis inhibitor, the typical daily dose of the cholesterol biosynthesis inhibitor is 0.1 to 80 mg/kg of mammalian weight per day administered in single or divided dosages, usually once or twice a day: for example, for HMG CoA reductase inhibitors, about 10 to about 40 mg per dose is given 1 to 2 times a day, giving a total daily dose of about 10 to 80 mg per day, and for the other cholesterol biosynthesis inhibitors, about 1 to 1000 mg per dose is given 1 to 2 times a day, giving a total daily dose of about 1 mg to about 2000 mg per day. The exact dose of any component of the combination to be administered is determined by the attending clinician and is dependent on the potency of the compound administered, the age, weight, condition and response of the patient.

Where the components of a combination are administered separately, the number of doses of each component given per day may not necessarily be the same, e.g. where one component may have a greater duration of activity, and will therefore need to be administered less frequently.

Since the present invention relates to the reduction of plasma cholesterol levels by treatment with a combination of active ingredients wherein said active ingredients may be administered separately, the invention also relates to combining separate pharmaceutical compositions in kit form. That is, a kit is contemplated wherein two separate units are combined: a cholesterol biosynthesis inhibitor pharmaceutical composition and a hydroxy substituted azetidinone cholesterol absorption inhibitor pharmaceutical composition. The kit will preferably include directions for the administration of the separate components. The kit form is particularly advantageous when the separate components must be administered in different dosage forms (e.g. oral and parenteral) or are administered at different dosage intervals.

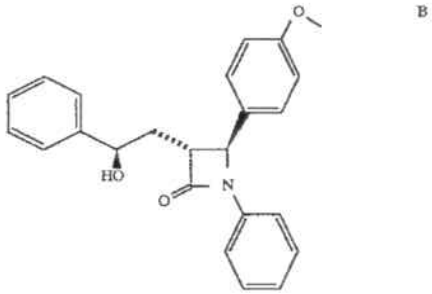
Following are examples of preparing compounds of formula I. The stereochemistry listed is relative stereochemistry unless otherwise noted. The terms cis and trans refer to the relative orientations at the azetidinone 3- and 4-positions unless otherwise indicated. The term "J" refers to the proton NMR coupling constant in hertz (Hz) between the 3- and 4-substituted protons of the azetidinone. All NMR data is of $CDCl_3$ solution unless otherwise indicated.

EXAMPLE 1



A

and



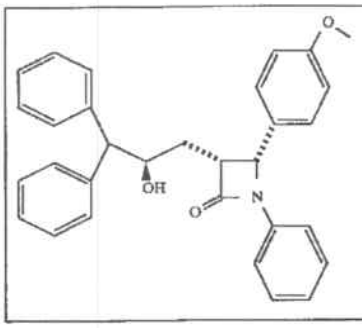
B

Freshly prepare a solution of lithium diisopropylamide (LDA) by dissolving diisopropylamine (1.19 g, 11.8 mmol) in anhydrous THF (20 ml) at −78° C. under argon. Add n-butyllithium (4.9 ml, 11.8 mmol, 2.4M in hexanes) and stir for 0.5 h at −78° C. To this cold solution add, 4-phenylbutyrolactone (1.75 g, 10.8 mmol) in THF (4 ml) over 0.25 h, keeping the reaction temperature below −65° C. Stir at −78° C. for 0.25 h, then add 4-methoxybenzylidine anisidine (2.33 g, 11.0 mmol) in THF (8 ml) over 1 h at −78° C. Warm the reaction slowly to −50° C. over 1 h. Quench the reaction at low temperature with 1N HCl (12 ml). Partition the reaction mixture between ether and 1N HCl, wash the ether layer with water, combine the ether extracts, dry over $MgSO_4$ and concentrate in vacuo. Crystallize the crude reaction residue (3.0 g) from EtOAc-ether to obtain 1.54 g of compound A. Reconcentrate the filtrate and chromatograph on silica gel 60, eluting with 4:1 EtOAc-hexane, and isolate additional compound A (0.385 g) as well as compound B (0.420 g).

Compound A: mp 218°–220° C.; IR 1730 cm-1; CI (M^+H) 374; J=5.9 Hz.

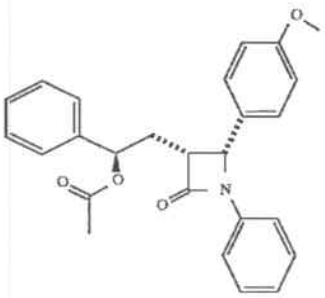
Compound B: mp 74°–76° C.; IR 1730 cm-1; CI (M^+H) 374; J=2.3 Hz.

Using a similar procedure and appropriate starting materials, prepare compound 1C:



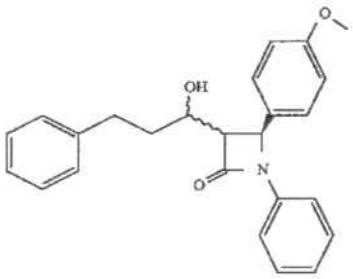
CI (M+H) 464, J = 2.3 Hz

EXAMPLE 2



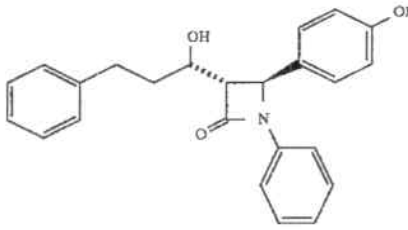
To a solution of compound A from Example 1 (0.5 g, 1.3 mmol) in anhydrous pyridine (2.7 ml), add acetic anhydride (0.63 ml, 6.7 mmol). Stir for 16 h, dilute with CH_2Cl_2 and wash 3× with 1N HCl, 1× with NaCl (sat'd) and 1× with water. Concentrate the organic layer to dryness and crystallize the residue from EtOAc to obtain the title compound (0.46 g), mp 167°–169° C.; IR 1745 cm-1; EI (M+) 415; J=5.9 Hz.

EXAMPLE 3



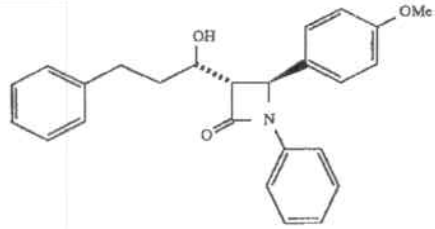
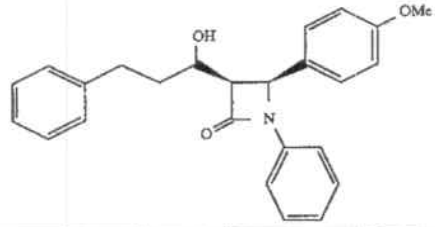
Freshly prepare a solution of lithium isopropylcyclohexylamide (LICA) by adding n-butyllithium (2.84 mL of a 1.6M solution) to a solution of isopropylcyclohexylamine (0.75 mL) in THF (100 mL) at –78° C. Dissolve N-phenyl-4-(4-methoxyphenyl)-2-azetidinone (1.0 g) in THF (8 mL) and slowly add to the LICA solution at –78° C. After stirring for 20 min, add hydrocinnamaldehyde (0.54 g) and stir the reaction mixture at –78° C. for 4 h. Quench the reaction with 10% $KHSO_4$ and extract the product with EtOAc. Separate the organic layer, wash with water and NaCl (sat'd). Concentrate the extract and purify the resultant residue on a silica gel 60 column, eluting with EtOAc:hexane (15:85) to obtain 1.15 g of product as a mixture of diastereomers. Separate the diastereomers by HPLC on a silica gel column to give three diastereomers 3A, 3B and 3C:

3A

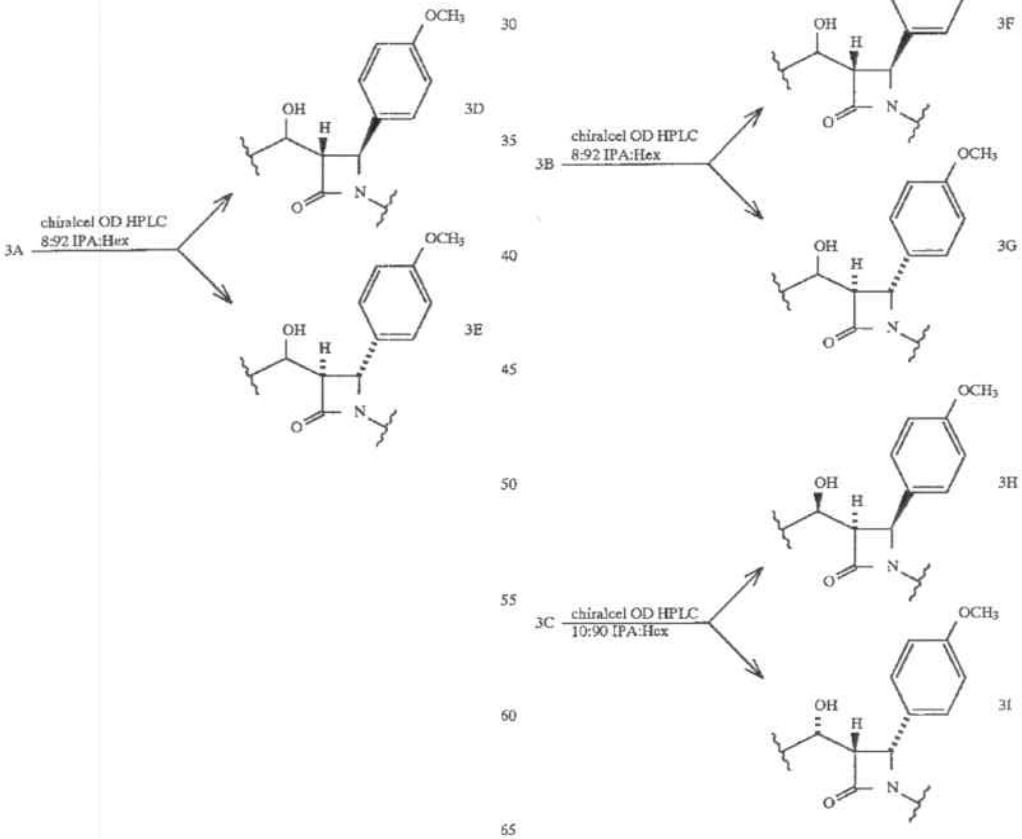


1H in $CDCl_3$: 7.32–7.18 (m, 11H); 7.08–6.99 (m, 1 H); 6.89 (d, J=9 Hz, 2H); 4.80 (d, J=2.4 Hz, 1H); 4.10–4.00 (m, 1H); 3.79 (s, 3H); 3.20–3.16 (m1 1H); 2.90–2.67 (m, 2H); 2.15–1.85 (m, 3H)

-continued

4B		1H in $CDCl_3$: 7.35–7.10 (m, 11H); 7.08–6.99 (m, 1H); 6.89 (d, J=9 Hz, 2H); 5.09 (d, J=2.4 Hz, 1H); 4.26–4.14 (m, 1H); 3.79 (s, 3H); 3.21–3.14 (m, 1H); 2.89–2.57 (m, 2H); 2.10–1.85 (m, 3H)
3C		1H in $CDCl_3$: 7.30–7.00 (m, 10H); 6.99 (d, J=8 Hz, 2H); 6.83 (d1 J=9 Hz, 2H); 5.12 (d, J=5.5 Hz, 1H); 3.82 (s, 3H); 3.75–3.63 (m, 1H); 3.52 (dd, J=9.5 Hz, 1H); 2.71–2.57 (m, 1H); 2.49–2.33 (m, 1H); 1.68–1.50 (m, 1H); 1.47–1.31 (m, 1H)

The 3A, 3B and 3C diastereomers were further separated according to the following reaction scheme, wherein partial structures are shown:



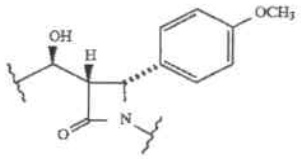
(The following CD spectra data [θ] are all obtained in CH_3OH.)

3D) $[\theta]_{227nM}$=+2.0×10^4 cm^2/dM; $[\theta]_{241nM}$=−4.6×10^4 cm^2/dM. Elemental analysis calc for $C_{25}H_{25}NO_3$.0.25 H_2O: C 76.6; H 6.56; N 3.57. found: C 76.66; H 6.49; N 3.64.

3E) $[\theta]_{227nM}$=−1.95×10^4 cm^2/dM; $[\theta]_{241nM}$=+4.45×10^4 cm^2/dM. Elemental analysis calc for $C_{25}H_{25}NO_3$.0.5 H_2O: C 75.73; H 6.61; N 3.53. found: C 75.66; H 6.41; N 3.60.

3F) $[\theta]_{226nM}$=+1.97×10^4 cm^2/dM; $[\theta]_{240nM}$=−5.22×10^4 cm^2/dM. Elemental analysis calc for $C_{25}H_{25}NO_3$: C 77.48; H 6.51; N 3.62. found: C 77.44; H 6.53; N 3.70.

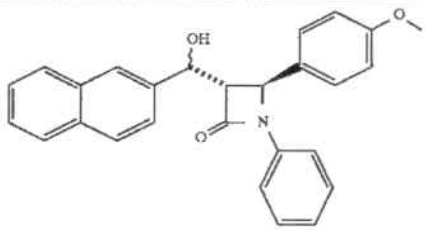
3G) $[\theta]_{226nM}$=−1.78×10^4 cm^2/dM; $[\theta]_{241nM}$=+4.78×10^4 cm^2/dM (CIMS 388 M$^+$H).



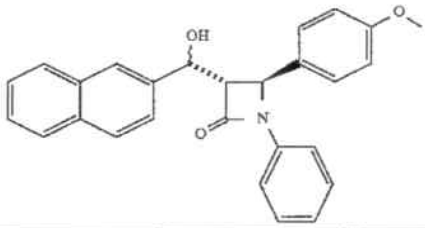
Using the procedure described for 3J, treat compound 3I to obtain 3K. [θ]222 nM=−3.4×10^3 cm^2/dM; [θ]240 nM=−5.6×10^4 cm^2/dM. $[\alpha]_D^{20}$=+167.2° (2.5 mg/ml CH_3OH).

Using the procedure described above for preparing compounds 3A and 3B, treat N-phenyl-4-(4-methoxyphenyl)-2-azetidinone with LICA followed by 2-naphthaldehyde to obtain the diastereomers 3L and 3M:

3L mp 137–138° C.

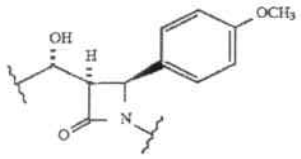


3M mp 150–151° C.



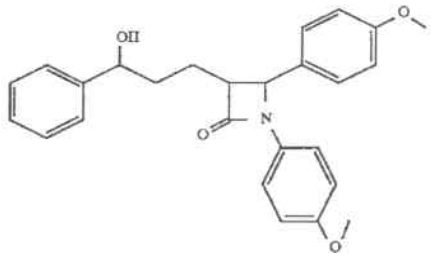
3H) $[\theta]_{226nM}$=+2.24×10^4 cm^2/dM; $[\theta]_{241nM}$=−5.4×10^4 cm^2/dM. $[\alpha]_D^{25}$=−54.40° (2.5 mg/ml CH_3OH). Elemental analysis calc for $C_{25}H_{25}NO_3$: C 77.48; H 6.51; N 3.62. found: C 77.11; H 6.50; N 3.72.

3I) $[\theta]_{226nM}$=−2.05×10^4 cm^2/dM; $[\theta]_{241nM}$=+5.2×10^4 cm^2/dM. (CIMS 388 M$^+$H).



Add DEAD (0.11 ml) to a solution of compound 3H (132 mg), PPh_3 (0.18 g) and HCO_2H (39 ml) in THF (5 ml). Stir at room temperature overnight, then partition the reaction mixture between Et_2O and H_2O. Wash (brine) and dry ($MgSO_4$) the organic layer and concentrate to dryness. Flash chromatograph the residue using EtOAc:Hex (1:4) to obtain the formate ester. Dissolve this in CH_3OH and add 4 drops of conc. HCl. After 4 h, concentrate in vacuo and flash chromatograph the residue using EtOAc:Hex (1:3) to obtain 3J. [θ]224 nM=+2.54×10^3 cm^2/dM; [θ]239 nM=+5.70×10^4 cm^2/dM. $[\alpha]_D^{20}$=−157.6° (2.5 mg/ml CH_3OH).

EXAMPLE 4



Method 1:

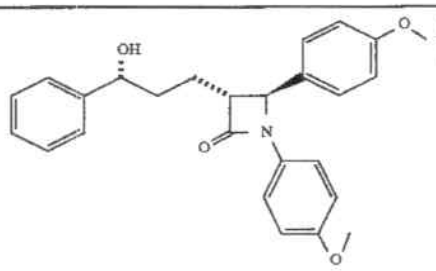
Step 1) To a refluxing solution of of 4-methoxybenzylidene anisidine (10.0 g, 41.5 mmol) and tributylamine (20.8 ml, 87 mmol) in toluene (100 ml), add 5-bromovaleroyl chloride (8.5 g, 43 mmol) in toluene (20 ml) dropwise over 2 h. Stir the reaction mixture at 80° C. for 12 h, cool to room temperature, wash 3× with 1N HCl, 1× with water and dry the organic layer over $MgSO_4$. Purifiy by silica gel chromatography, eluting with ethyl acetate:hexane (4:1) to obtain 5.1 g of (3R, 4S)-1,4-bis-(4-methoxyphenyl)-3-(3-bromopropyl)-2-azetidinone (relative stereochemistry), mp 70°–73° C.; EI (M$^+$) 404; J=2.3 Hz.

Step 2) To a solution of the product of step 1 (5.1 g, 12.6 mmol) in $(CH_3)_2SO$ (20 ml), add $(CH_3)_3N(O)$ (2.39 g, 31.9 mmol). Heat the mixture at 60° C. for 3 h, cool to room temperature, dilute with EtOAc, and wash 3× with water. Combine the aqueous fractions and extract with EtOAc. Combine the organic fractions and concentrate. Purify the crude product by silica gel chromatography, eluting with EtOAc:hexane (1:1) to obtain 1.4 g (3R, 4S)-1,4-bis-(4-methoxyphenyl)-2-oxo-3-azetidine-propanal (relative stereochemistry), an oil; EI (M^+) 339; J=2.3 Hz.

eluting with EtOAc:hexane (2:1) to obtain 0.372 g of the title compound (mix of diastereomers) as an oil. CI (M^+H) 418.

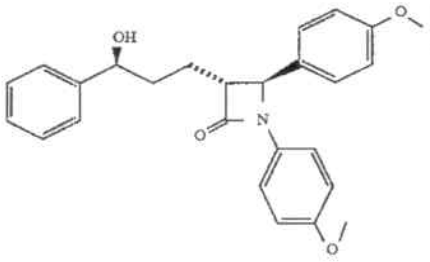
Separation of diastereomers: Apply the diastereomeric mixture from step 3 to a Chiralcel OD (Chiral Technologies Corp, PA) chromatography column, eluting with hexane: ethanol (9:1) to obtain enantiomerically pure (>98%) diastereomers as follows:

4A



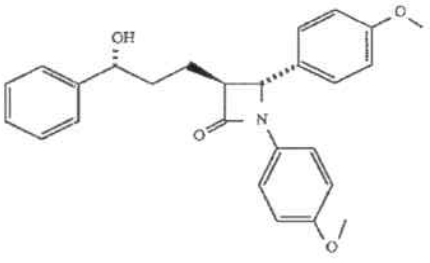
Oil; $[\alpha]_D^{22}$=+8.3°, conc.=3 mg/ml in MeOH; CI (M+H) 418. J=2.1 Hz.

4B



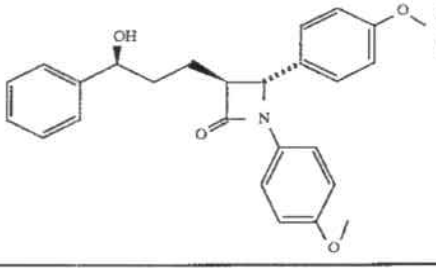
Oil; $[\alpha]_D^{22}$=+33.1°, conc.= 3 mg/ml in MeOH; CI (M+H) 418. J=2.1 HZ.

4C



Oil; $[\alpha]_D^{22}$=−8.0°, conc.=3 mg/ml in MeOH; CI (M+H) 418. J=2.1 Hz.

4D



Oil; $[\alpha]_D^{22}$=−29.5°, conc.=3 mg/ml in MeOH; CI (M+H) 418. J=2.1 Hz.

Step 3) To a solution of the product of step 2 (0.734 g, 2.2 mmol) in THF (4 ml) at 0° C., add phenylmagnesium bromide (2.4 ml, 2.4 mmol, 1.0M in THF) over 0.25 h. After 1 h at 0° C., add water (5 ml), separate the layers, wash the organic layer 1× with 1N HCl, dry with $MgSO_4$ and concentrate to an oil. Purify by silica gel chromatography,

Method 2:

Step 1) To a solution of 1,4-(S)-bis(4-methoxyphenyl)-3-(3(R)-phenylpropyl)-2-azetidinone (5.04 g, 0.013 mole) in CCl_4 (20 ml) at 80° C., add NBS (2.76 g, 0.0155 mole) and benzoyl peroxide (0.24 g, 1.0 mmole) in three equal portions over 1 h. Follow the reaction by TLC (4:1 hexane: EtOAc). Cool the reaction to 22° C., add $NaHSO_4$, separate the layers

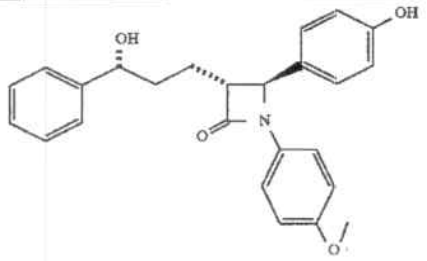
and wash the organic layer 3× with water. Concentrate the organic layer to obtain the crude product.

CI (M^+H) 480; ^1H in $CDCl_3$ δPhCH(OH)=5.05 ppm.

Step 2) Dissolve the crude product of Step 1 in CH_2Cl_2 (30 ml) and add 40% n-$BuNOC(O)CF_3$ in water (30 ml). Reflux the biphasic reaction for 24 h, cool, separate the layers and wash the organic layer 6× with water. Concentrate the organic layer to dryness and immediately redissolve the residue in ethanol saturated with NH_3 (10 ml). After 1 h, concentrate the reaction mixture and partially purify by silica gel chromatography. Further purify by HPLC to obtain a 1:1 mixture of compounds 4A and 4B. The mixture can be further purified on a Chiracel OD column to obtain 4A and 4B separately as characterized above.

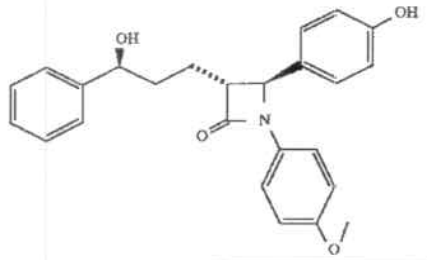
Using the procedure described in Example 4, Method 2, with 4(S)-(4-acetoxyphenyl)-3(R)-(3-phenylpropyl)-1-(4-methoxy-phenyl)-2-azetidinone as the starting material, prepare the following compounds:

4E



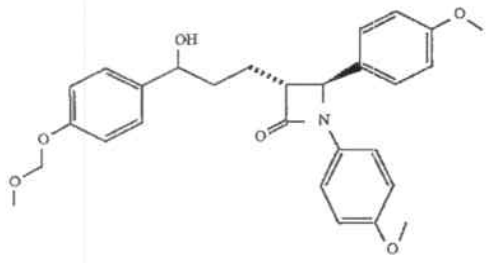
mp 87–90° C.;
HRMS calc'd for $C_{25}H_{25}NO_4$= 403.1797, found 403.1785;
^1H in $CDCl_3$ δ PhCH(OH)=4.82 ppm.

4F



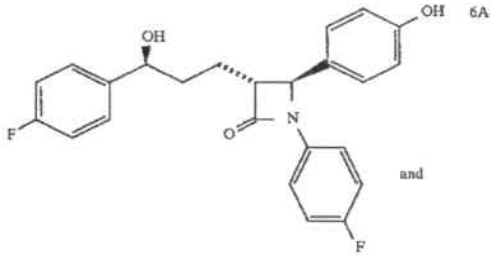
HRMS calc'd for $C_{25}H_{25}NO_4$= 403.1797, found 403.1787;
^1H in $CDCl_3$ δ PhCH(OH)=4.78 ppm.

EXAMPLE 5

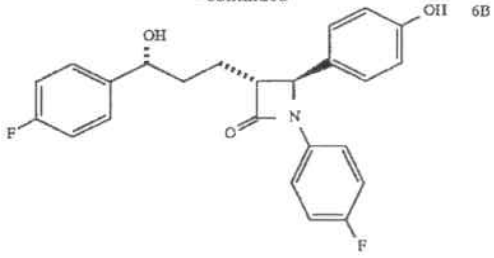


To a solution of the product of step 2 of Example 4 (0.230 g, 0.68 mmol) in THF (2 ml), add the reagent derived from treatment of 4-methoxymethoxyphenyl bromide (0.159 g, 0.736 mmol) in THF (4 ml) at −78° C. with sec-butyllithium (0.6 ml, 0.78 mol, 1.3M in hexanes), followed by $CeCl_3$ (0.186 g, 0.75 mmol). After 4 h, extract the product and purify by chromatography in a manner similar to that described in step 3 of Example 4 to obtain 0.05 g of the title compound (mix of diastereomers) as an oil. CI (M^+H) 478.

EXAMPLE 6



6A and



6B

Step 1): To a solution of (S)-4-phenyl-2-oxazolidinone (41 g, 0.25 mol) in CH_2Cl_2 (200 ml), add 4-dimethylaminopyridine (2.5 g, 0.02 mol) and triethylamine (84.7 ml, 0.61 mol) and cool the reaction to 0° C. Add methyl-4-(chloroformyl)butyrate (50 g, 0.3 mol) as a solution in CH_2Cl_2 (375 ml) dropwise over 1 h, and allow the reaction to warm to 22° C. After 17 h, add water and H_2SO_4 (2N, 100 ml), separate the layers, and wash the organic layer sequentially with NaOH (10%), NaCl (sat'd)

and water. Dry the organic layer over $MgSO_4$ and concentrate to obtain a semicrystalline product.

Step 2): To a solution of $TiCl_4$ (18.2 ml, 0.165 mol) in CH_2Cl_2 (600 ml) at 0° C., add titanium isopropoxide (16.5 ml, 0.055 mol). After 15 min, add the product of Step 1 (49.0 g, 0.17 mol) as a solution in CH_2Cl_2 (100 ml). After 5 min., add diisopropylethylamine (DIPEA) (65.2 ml, 0.37 mol) and stir at 0° C. for 1 h, cool the reaction mixture to −20° C., and add 4-benzyloxybenzylidine(4-fluoro)aniline (114.3 g, 0.37 mol) as a solid. Stir the reaction vigorously for 4 h at −20° C., add acetic acid as a solution in CH_2Cl_2 dropwise over 15 min, allow the reaction to warm to 0° C., and add H_2SO_4 (2N). Stir the reaction an additional 1 h, separate the layers, wash with water, separate and dry the organic layer. Crystallize the crude product from ethanol/water to obtain the pure intermediate.

Step 3): To a solution of the product of Step 2 (8.9 g, 14.9 mmol) in toluene (100 ml) at 50° C., add N,O-bis (trimethylsilyl)acetamide (BSA) (7.50 ml, 30.3 mmol). After 0.5 h, add solid TBAF (0.39 g, 1.5 mmol) and stir the reaction at 50° C. for an additional 3 h. Cool the reaction mixture to 22° C., add CH_3OH (10 ml), wash the reaction mixture with HCl (1N), $NaHCO_3$ (1N) and NaCl (sat'd.), and dry the organic layer over $MgSO_4$.

Step 4): To a solution of the product of Step 3 (0.94 g, 2.2 mmol) in CH_3OH (3 ml), add water (1 ml) and $LiOH.H_2O$ (102 mg, 2.4 mmole). Stir the reaction at 22° C. for 1 h and add additional $LiOH.H_2O$ (54 mg, 1.3 mmole). After a total of 2 h, add HCl (1N) and EtOAc, separate the layers, dry the organic layer and concentrate in vacuo. To a solution of the resultant product (0.91 g, 2.2 mmol) in CH_2Cl_2 at 22° C., add ClCOCOCl (0.29 ml, 3.3 mmol) and stir for 16 h. Remove the solvent in vacuo.

Step 5): To an efficiently stirred suspension of 4-fluorophenylzinc chloride (4.4 mmol) prepared from 4-fluorophenylmagnesium bromide (1M in THF, 4.4 ml, 4.4 mmol) and $ZnCl_2$ (0.6 g, 4.4 mmol) at 4° C., add tetrakis (triphenylphosphine)palladium (0.25 g, 0.21 mmol) and the product of Step 4 (0.94 g, 2.2 mmol) as a solution in THF (2 ml). Stir the reaction for 1 h at 0° C. and then for 0.5 h at 22° C. Add HCl (1N, 5 ml) and extract with EtOAc. Concentrate the organic layer to an oil and purify by silica gel chromatography to obtain 1-(4-fluorophenyl)-4(S)-(4-hydroxyphenyl)-3(R)-(3-oxo-3-phenylpropyl)-2-azetidinone: HRMS calc'd for $C_{24}H_{19}F_2NO_3$=408.1429, found 408.1411.

Step 6): To the product of Step 5 (0.95 g, 1.91 mmol) in THF (3 ml), add (R)-tetrahydro-1-methyl-3,3-diphenyl-1H, 3H-pyrrolo-[1,2-c][1,3,2] oxazaborole (120 mg, 0.43 mmol) and cool the mixture to −20° C. After 5 min, add borohydride-dimethylsulfide complex (2M in THF, 0.85 ml, 1.7 mmol) dropwise over 0.5 h. After a total of 1.5 h, add CH_3OH followed by HCl (1N) and extract the reaction mixture with EtOAc to obtain 1-(4-fluorophenyl)-3(R)-[3 (S)-(4-fluorophenyl)-3-hydroxypropyl)]-4(S)-[4-(phenylmethoxy)phenyl]-2-azetidinone (compound 6A-1) as an oil. ^1H in $CDCl_3$ δH3=4.68. J=2.3 Hz. CI (M^+H) 500.

Use of (S)-tetra-hydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo-[1,2-c][1,3,2] oxazaborole gives the corresponding 3(R)-hydroxypropyl azetidinone (compound 6B-1). ^1H in $CDCl_3$ δH3=4.69. J=2.3 Hz. CI (M^+H) 500.

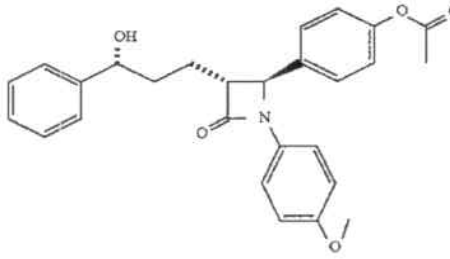
To a solution of compound 6A-1 (0.4 g, 0.8 mmol) in ethanol (2 ml), add 10% Pd/C (0.03 g) and stir the reaction under a pressure (60 psi) of H_2 gas for 16 h. Filter the reaction mixture and concentrate the solvent to obtain compound 6A. Mp 164°–166° C.; CI (M^+H) 410. $[\alpha]_D^{25}$=−28.1° (c 3 CH_3OH) . Elemental analysis calc'd for $C_{24}H_{21}F_2NO_3$: C 70.41; H 5.17; N 3.42; found C 70.25; H 5.19; N 3.54.

Similarly treat compound 6B-1 to obtain compound 6B. Mp 129.5°–132.5° C.; CI (M^+H) 410. Elemental analysis calc'd for $C_{24}H_{21}F_2NO_3$: C 70.41; H 5.17; N 3.42; found C 70.30; H 5.14; N 3.52.

Step 6') (Alternative): To a solution of the product of Step 5 (0.14 g, 0.3 mmol) in ethanol (2 ml), add 10% Pd/C (0.03 g) and stir the reaction under a pressure (60 psi) of H_2 gas for 16 h. Filter the reaction mixture and concentrate the solvent to afford a 1:1 mixture of compounds 6A and 6B.

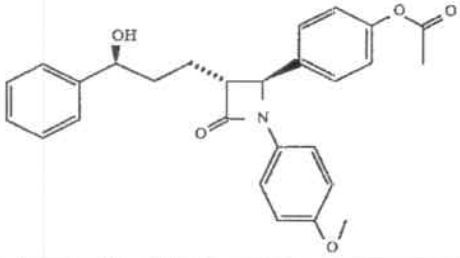
Using appropriate starting materials and following the procedure of steps 1–6, prepare the following compounds:

6C

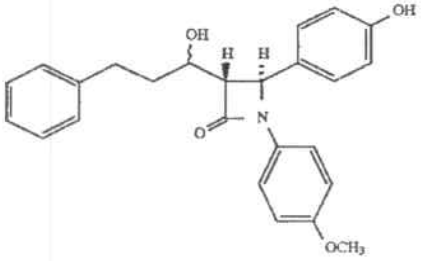


CI (M+H) 446;
HRMS calc'd for $C_{27}H_{27}NO_5$= 445.1904, found 445.1890

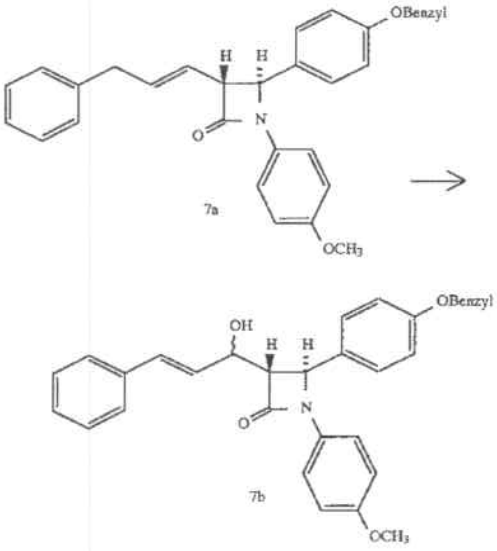
-continued

6D		CI (M+H) 446; HRMS calc'd for $C_{25}H_{25}NO_4$= 445.1904, found 445.1911

EXAMPLE 7



Step 1):



To a solution of 7a (1.0 g, 2.1 mmol) in dioxane (10 ml), add SeO_2 (1.33 g, 11.98 mmol) and water (0.25 ml, 14 mmol), and heat the reaction to 100° C. After 1 h, cool the reaction to room temperature and isolate by extraction the crude product as a diastereomeric mixture (1:2) of alcohols 7b-A and 7b-B. Purify by HPLC on a Dynamax silica column to separate diastereomers 7b-A and 7b-B.

Diastereomer 7b-A (R): oil; $J_{3,4}$=2.3 Hz, δ C H(OH)=4.86 (t); HRMS $C_{32}H_{29}NO_4$ calc.: 491.2097; found: 491.2074.

Diastereomer 7b-B (S): oil; $J_{3,4}$=2.3 Hz, δ C H(OH)=5.06 (t);

HRMS $C_{32}H_{29}NO_4$ calc.: 491.2097; found: 491.2117.

Step 2): To a solution of diastereomer A from step 1 (58 mg, 0.12 mmol) in EtOAc (2 ml), add 10% Pd on carbon (20 mg) and stir at 22° C. under H_2 gas (14 psi) for 12 h. Filter and concentrate to obtain the title compound as a semisolid, m.p. 90°–92° C. $J_{3,4}$=2.3 Hz, δ CH(OH)=4.1 (m); HRMS $C_{25}H_{25}NO_4$ calc.: 403.1783; found: 403.1792.

EXAMPLE 8

To a solution of the product of Example 4A (90 mg, 0.2 mmol) in CH_2Cl_2, add acetyl chloride (80 mg, 1.0 mmol) and pyridine (B mg, 0.1 mmol) and stir at room temperature for 1 h. Add water, separate the layers and isolate the corresponding acetoxy compound, 8A. In a similar manner, treat the products of Examples 4B, 6B and 6A to obtain the following compounds 8B, 8C and 8D, respectively:

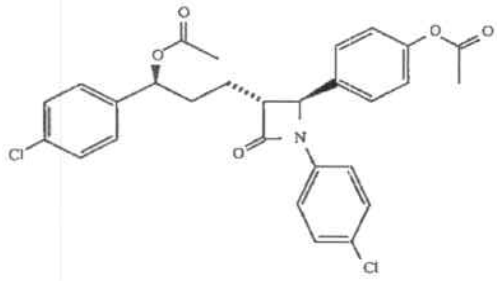
8A: 1,4(S)-bis(4-methoxyphenyl)-3(R)-(3(R)-acetoxy-3-phenylpropyl)-2-azetidinone. CI (M^+H) 460; HRMS $C_{28}H_{29}NO_5$ calc.: 459.2044; found: 459.2045.

8B: 1,4(S)-bis(4-methoxyphenyl)-3(R)-(3(S)-acetoxy-3-phenylpropyl)-2-azetidinone. CI (M^+H) 460; HRMS $C_{28}H_{29}NO_5$ calc.: 459.2044; found: 459.2048.

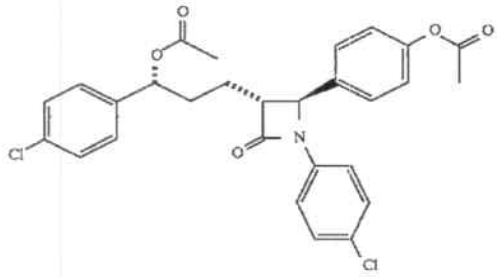
8C: 4(S)-(4-acetyloxyphenyl)-3(R)-(3(R)-acetyloxy-3-(4-fluorophenyl)propyl)-1-(4-fluorophenyl)-2-azetidinone. FAB MS 493.4; HRMS $C_{28}H_{25}F_2NO_5$ calc.: 493.1695; found: 493.1701.

8D: 4(S)-(4-acetyloxyphenyl)-3(R)-(3(S)-acetyloxy-3-(4-fluorophenyl)propyl)-1-(4-fluorophenyl)-2-azetidinone. FAB MS 493.4; HRMS $C_{28}H_{25}F_2NO_5$ calc.: 493.1695; found: 493.1694.

Using appropriate starting materials in the procedure of Example 6, prepare 1-(4-chlorophenyl)-3(R)-(hydroxy-3-(4-chlorophenyl)propyl)-4(S)-(4-hydroxyphenyl)-2-azetidinone. Using the procedure of Example 8, prepare the following diacetates 8E and 8F:

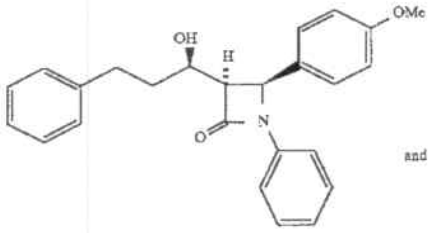
8E 

CI (M+H) 527;
^{1}H $CDCl_3$ δ H3'=4.65

8F 

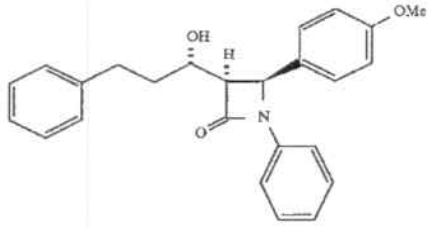
CI (M+H) 527;
^{1}H $CDCl_3$ δ H3'=4.67

EXAMPLE 9



3H

and



3K

Step 1: Add pyridinium chlorochromate (2.4 g, 11 mmoles) and CH_3CO_2Na (approx. 20 mg) to a solution of 1-phenyl-3-(3-phenyl-1-hydroxypropyl)-4-(4-methoxyphenyl)-2-azetidinone (2.35 g, 6.1 mmoles) in CH_2Cl_2. Stir at room temperature for 18 h, then add silica gel (40 g) and concentrate to dryness. Flash chromatograph the residue using EtOAc:Hex (1:4) to obtain an oil. (1.98 g, yield=85%). ^{1}H NMR 2.85–2.95 (m, 3H), 3.15 (m, 1H), 3.80 (s, 3H), 4.10 (d, 1H, J 2.6), 5.42 (1 H, d, J 2.6), 6.85 (dd, 2H, J 2, 8), 7.05 (m, 1 H), 7.2–7.35 (m, 11 H).

Step 2: To a solution of the product of Step 1 (1.78 g, 4.62 mmoles) in THF at −10° C., add NaH (115 mg ,4.8 mmoles). After 15 min., add NBS (865 mg, 4.85 mmoles) and stir for 20 min., then add 1N HCl and partition between EtOAc and brine. Separate the organic layer, dry ($MgSO_4$) and concentrate to give an oil. Flash chromatograph the oil using EtOAc:Hex (1:10) to collect first 9a as a foamy solid (830 mg, y=39%/, FAB MS 466/464, M^+H), and then 9b as a colorless solid (1.1 g, y=51%, FAB MS 466/464, M^+H).

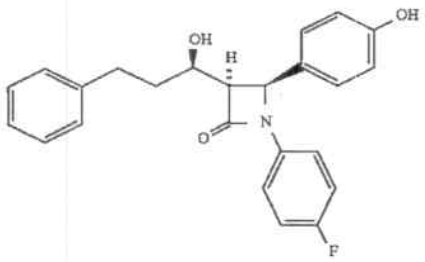
Step 3a: Add $Mg(OCOCF_3)_2.CF_3CO_2H$ (7.3 ml of 1M solution in Et_2O,) to a solution of 9a (0.68 g, 1.46 mmoles) in THF (5 ml) at −50° C. Stir the reaction 5 min., then add t-Bu-NH_2-BH_3 (254 mg, 2.92 mmole). After 15 min., allow the reaction to warm to 0° C. over 20 min., add 1N HCl and concentrate in vacuo. Partition the residue between EtOAc and brine. Concentrate the organic layers and dissolve the resultant oil in CH_2Cl_2:CH_3OH (1:1) and add ethanolamine (approx 2 mmoles). After 15 min., concentrate the reaction mixture and partition the residue with EtOAc:1N HCl. Wash (brine) and dry ($MgSO_4$) the organic layer to obtain an oil. Purify this oil by flash chromatography using EtOAc:Hex (1:4) to obtain compound 9a-1, a colorless solid, as a 4:1 mix of diastereomers. 0.52 g, y=76%, SIMS 468/466 (M^+H).

Step 3b: Using compound 9b as the starting material, use a procedure similar to Step 3a with CH_2Cl_2 as solvent for the preparation of 9b-1 in 80% yield as a 13:1 mixture of diastereomers (SIMS 468/466 M^+H).

Step 4a: Add a solution of 9a-1 (0.27 g, 0.58 mmoles) and AIBN (18 mg, 0.12 mmole) in toluene (40 ml) dropwise over 40 min. to a solution of $(TMS)_3SiH$ (1.0 ml) in toluene at 80° C. After 1 h, add more AIBN (5 mg) and continue at 80° C. for 1.5 h. Cool and concentrate the reaction mixture, dissolve the residue in CH_3CN and wash 3× with hexane. Concentrate the CH_3CN layer to give the title compound as a racemic mixture (0.25 g). Purify this oil by HPLC using a Chiralcel OD column to obtain 3H (major) and 3J (minor).

Step 4b: Use the procedure of Step 4a, starting with compound 9b-1 to obtain an oil. Purify this by flash chromatography using EtOAc:Hex (1:3) to collect the racemic title compound (y=70%). Purify this oil by HPLC using a Chiralcel OD column to obtain 3J (major) and 3H (minor).

EXAMPLE 10



Step 1: Follow the procedure of Example 3, using 1-(4-fluorophenyl-4-(4-t-butyidimethylsilyloxyphenyl)-2-azetidinone to obtain 1-(4-fluorophenyl-3-(3-phenyl-1-hydroxypropyl) 4-(4-t-butyldimethylsilyl-oxyphenyl)-2-azetidinone.

Step 2: Treat a solution of the cis-azetidinone of Step 1 (0.25 g) in CH_3CN (21 ml) with 48% aqueous HF (2.5 ml). After 18 h, dilute the reaction mixture with cold H_2O and extract with Et_2O. Wash (2× H_2O, dilute $NaHCO_3$ and brine), dry ($MgSO_4$) and concentrate the Et_2O layer. Crystallize the residue from EtOAc:hexane (1:2) to obtain the title compound as colorless needles (123 mg, y=64%), mp 168°–171° C. Elemental analysis calc for $C_{24}H_{22}O_3FN$: C 73.64; H 5.66; N 3.58. found C 73.32; H 5.65; N 3.68.

The following formulations exemplify some of the dosage of this invention. In each the term "active compound" designates a compound of formula I.

EXAMPLE A

Tablets

No.	Ingredient	mg/tablet	mg/tablet
1	Active Compound	100	500
2	Lactose USP	122	113
3	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4	Corn Starch, Food Grade	45	40
5	Magnesium Stearate	3	7
	Total	300	700

Method of Manufacture

Mix Item Nos. 1 and 2 in suitable mixer for 10–15 minutes. late the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., ¼", 0.63 cm) if necessary. Dry the damp granules. Screen the dried granules if necessary and mix with Item No. 4 and mix for 10–15 minutes. Add Item No. 5 and mix for 1–3 minutes. Compress the mixture to appropriate size and weight on a suitable tablet machine.

EXAMPLE B

Capsules

No.	Ingredient	mg/tablet	mg/tablet
1	Active Compound	100	500
2	Lactose USP	106	123
3	Corn Starch, Food Grade	40	70

-continued

Capsules

No.	Ingredient	mg/tablet	mg/tablet
4	Magnesium Stearate NF	4	7
	Total	250	700

Method of Manufacture

Mix Item Nos. 1, 2 and 3 in a suitable blender for 10–15 minutes. Add Item No. 4 and mix for 1–3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

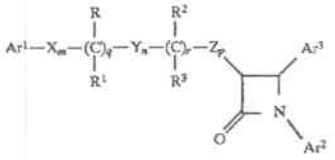
Representative formulations comprising a cholesterol biosynthesis inhibitor-are well known in the art. It is contemplated that where the two active ingredients are administered as a single composition, the dosage forms disclosed above for substituted azetidinone compounds may readily be modified using the knowledge of one skilled in the art.

Using the test procedures described above, the following in vivo data were obtained for the exemplified compounds. Data is reported as percent change (i.e., percent reduction in cholesterol esters) versus control, therefore, negative numbers indicate a positive lipid-lowering effect.

	% Reduction		
Ex. #	Serum Cholest.	Cholest. Esters	Dose mg/kg
1A	−23	0	50
1B	−15	−39	50
1C	14	0	50
2	0	0	50
3A	−31	−69	50
3C	−60	−92	50
3D	−17	−61	10
3E	0	0	10
3F	−29	−77	10
3G	−16	−38	10
3H	−41	−86	10
3I	0	−22	10
3J	0	0	3
3K	0	0	10
3L	−15	−21	10
3M	0	−22	10
4A	0	−54	5
4B	−37	−89	8
4C	−12.5	0	3
4D	9	0	7
4E	0	−46	3
4F	−29	−95	3
5	0	−64	10
6A	−59	−95	1
6A-1	−43	−93	1
6B	−40	−92	3
6C	0	−48	3
6D	−46	−95	10
8A	0	−44	3
8B	−50	−95	3
8C	−14	−37	1
8D	−49	−98	1
8E	−22	−66	3
8F	−43	−94	1
10	−26	−77	3

We claim:

1. A pharmaceutical composition for the treatment or prevention of atherosclerosis, or for the reduction of plasma cholesterol levels, comprising an effective amount of a compound represented by the formula I



or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 and Ar^2 are independently selected from the group consisting of aryl and R^4-substituted aryl;

Ar^3 is aryl or R^5-substituted aryl;

X, Y and Z are independently selected from the group consisting of —CH_2—, —CH(lower alkyl)— and —C(dilower alkyl)—;

R and R^2 are independently selected from the group consisting of —OR^6, —$O(CO)R^6$, —$O(CO)OR^9$ and —$O(CO)NR^6R^7$;

R^1 and R^3 are independently selected from the group consisting of hydrogen, lower alkyl and aryl;

q is 0 or 1; r is or 1; m, n and p are independently 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1, 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5;

R^4 is 1–5 substituents independently selected from the group consisting of lower alkyl, —OR^6, —$O(CO)R^6$, —$O(CO)OR^9$, —$O(CH_2)_{1-5}OR^6$, —$O(CO)NR^6R^7$, —NR^6R^7, —$NR^6(CO)R^7$, —$NR^6(CO)OR^9$, —$NR^6(CO)NR^7R^8$, —$NR^6SO_2R^9$, —$COOR^6$, —$CONR^6R^7$, —COR^6, —$SO_2NR^6R^7$, $S(O)_{0-2}R^9$, —$O(CH_2)_{1-10}$—$COOR^6$, —$O(CH_2)_{1-10}CONR^6R^7$, —(lower alkylene)$COOR^6$, —CH═CH—$COOR^6$, —CF_3, —CN, —NO_2 and halogen;

R^5 is 1–5 substituents independently selected from the group consisting of —OR^6, —$O(CO)R^6$, —$O(CO)OR^9$, —$O(CH_2)$l $5OR^6$, —$O(CO)N$ R^6R^7, —NR^6R^7, —$NR^6(CO)R^7$, —$NR^6(CO)OR^9$, —$NR^6(CO)NR^7R^8$, —$NR^6SO_2R^9$, —$COOR^6$, —$CONR^6R^7$, —COR^6, —$SO_2NR^6R^7$, $S(O)_{0-2}R^9$, —$O(CH_2)_{1-10}$—$COOR^6$, —$O(CH_2)_{1-10}CONR^6R^7$, —(lower alkylene)$COOR^6$ and —CH═CH—$COOR^6$;

R^6, R^7 and R^8 are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

R^9 is lower alkyl, aryl or aryl-substituted lower alkyl;

in combination with an HMG CoA reductase inhibitor in a pharmaceutically acceptable carrier.

2. A pharmaceutical composition of claim 1 wherein, in the compound of formula I, Ar^1 is phenyl or R^4-substituted phenyl, wherein R^4 is halogen; Ar^2 is phenyl or R^4-substituted phenyl, wherein R^4 is halogen or —OR^6, wherein R^6 is lower alkyl or hydrogen; Ar^3 is R^5-substituted phenyl, wherein R^5 is —OR^6, wherein R^6 is lower alkyl or hydrogen; X, Y, and Z are each —CH_2—; R^1 and R^3 are each hydrogen; R and R^2 are each —OR^6, wherein R^6 is hydrogen; and the sum of m, n, p, q and r is 2, 3 or 4.

3. A composition of claim 1 wherein the HMG CoA reductase inhibitor is selected from the group consisting of lovastatin, pravastatin, fluvastatin, simvastatin and atorvastatin.

4. A composition of claim 1 wherein the compound of formula I is selected from the group consisting of

rel 3(R)—(2(R)-hydroxy-2-phenylethyl)-4(R)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

rel 3(R)-(2(R)-hydroxy-2-phenylethyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

3(S)-(1(S)-hydroxy-3-phenylpropyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

3(S)-(1(R)-hydroxy-3-phenylpropyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

3(R)-(1(R)-hydroxy-3-phenylpropyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

3(R)-(3(R)-hydroxy-3-phenylpropyl)-1,4(S)-bis-(4-methoxyphenyl)-2-azetidinone;

3(R)-(3(S)-hydroxy-3-phenylpropyl)-1,4(S)-bis-(4-methoxyphenyl)-2-azetidinone;

4(S)-(4-hydroxyphenyl)-3(R)-(3(R)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone;

4(S)-(4-hydroxyphenyl)-3(R)-(3(S)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone;

rel 3(R)-[3(RS)-hydroxy-3-[4-(methoxymethoxy)-phenyl]propyl]-1,4(S)-bis-(4-methoxyphenyl)-2-azetidinone;

1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl)]-4(S)-(4-hydroxyphenyl)-2-azetidinone;

1-(4-fluorophenyl)-3(R)-[3(R)-(4-fluorophenyl)-3-hydroxypropyl)]-4(S)-(4-hydroxyphenyl)-2-azetidinone;

4(S)-[4-(acetyloxy)phenyl]-3(R)-(3(R)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone;

4(S)-[4-(acetyloxy)phenyl]-3(R)-(3(S)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone;

1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl)]-4(S)-[4-(phenylmethoxy)phenyl]-2-azetidinone;

3(R)-[3(R)-acetyloxy)-3-phenylpropyl]-1,4(S)-bis-(4-methoxy-phenyl)-2-azetidinone;

3(R)-[3(S)-acetyloxy)-3-phenylpropyl]-1,4(S)-bis-(4-methoxy-phenyl)-2-azetidinone;

3(R)-[3(R)-(acetyloxy)-3-(4-fluorophenyl)propyl]-4(S)-[4-(acetyloxy)-phenyl]-1-(4-fluorophenyl)-2-azetidinone;

3(R)-[3(S)-(acetyloxy)-3-(4-fluorophenyl)propyl]-4(S)-[4-(acetyloxy)-phenyl]-1-(4-fluorophenyl)-2-azetidinone;

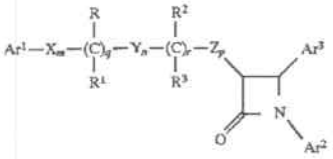
3(R)-[3(R)-(acetyloxy)-3-(4-chlorophenyl)propyl]-4(S)-[4-(acetyloxy)phenyl]-11-(4-chlorophenyl)-2-azetidinone;

3(R)-[3(S)-(acetyloxy)-3-(4-chlorophenyl)propyl]-4(S)-[4-(acetyloxy)phenyl]-1-(4-chlorophenyl)-2-azetidinone; and

rel 1-(4-fluorophenyl)-4(S)-(4-hydroxyphenyl)-3(R)-(1(R)-hydroxy-3-phenylpropyl)-2-azetidinone.

5. A composition of claim 1 comprising a combination of 1-(4-fluorophenyl)-3(R)-[3(R)-(4-fluorophenyl)-3-hydroxypropyl)]-4(S)-(4-hydroxyphenyl)-2-azetidinone and lovastatin, pravastatin, fluvastatin, simvastatin or atorvastatin.

6. A method of treating or preventing atherosclerosis or reducing plasma cholesterol levels comprising administering to a mammal in need thereof an effective amount of a compound represented by the formula I



I

or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 and Ar^2 are independently selected from the group consisting of aryl and R^4-substituted aryl;

Ar^3 is aryl or R^5-substituted aryl;

X, Y and Z are independently selected from the group consisting of —CH_2—, —CH(lower alkyl)— and —C(dilower alkyl)—;

R and R^2 are independently selected from the group consisting of —OR^6, —$O(CO)R^6$, —$O(CO)OR^9$ and —$O(CO)NR^6R^7$;

R^1 and R^3 are independently selected from the group consisting of hydrogen, lower alkyl and aryl;

q is 0 or 1; r is 0 or 1; m, n and p are independently 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1, 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5;

R^4 is 1–5 substituents independently selected from the group consisting of lower alkyl, —OR^6, —$O(CO)R^6$, —$O(CO)OR^9$, —$O(CH_2)_{1-5}OR^6$, —$O(CO)NR^6R^7$, —NR^6R^7, —$NR^6(CO)R^7$, —$NR^6(CO)OR^9$, —$NR^6(CO)NR^7R^8$, —$NR^6SO_2R^9$, —$COOR^6$, —$CONR^6R^7$, —COR^6, —$SO_2NR^6R^7$, $S(O)_{0-2}R^9$, —$O(CH_2)_{1-10}$—$COOR^6$, —$O(CH_2)_{1-10}CONR^6R^7$, —(lower alkylene)$COOR^6$, —CH═CH—$COOR^6$, —CF_3, —CN, —NO_2 and halogen;

R^5 is 1–5 substituents independently selected from the group consisting of —OR^6, —$O(CO)R^6$, —$O(CO)OR^9$, —$O(CH_2)_{1-5}OR^6$, —$O(CO)NR^6R^7$, —NR^6R^7, —$NR^6(CO)R^7$, —$NR^6(CO)OR^9$, —$NR^6(CO)NR^7R^8$, —$NR^6SO_2R^9$, —$COOR^6$, —$CONR^6R^7$, —COR^6, —$SO_2NR^6R^7$, $S(O)_{0-2}R^9$, —$O(CH_2)_{1-10}$—$COOR^6$, —$O(CH_2)_{1-10}CONR^6R^7$, —(lower alkylene)$COOR^6$ and —CH═CH—$COOR^6$;

R^6, R^7 and R^8 are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

R^9 is lower alkyl, aryl or aryl-substituted lower alkyl; in combination with an effective amount of a cholesterol biosynthesis inhibitor selected from the group consisting of HMG CoA reductase inhibitors.

7. A method of claim 6 wherein, in the compound of formula I, Ar^1 is phenyl or R^4-substituted phenyl, wherein R^4 is halogen; Ar^2 is phenyl or R^4-substituted phenyl, wherein R^4 is halogen or —OR^6, wherein R^6 is lower alkyl or hydrogen; Ar^3 is R^5-substituted phenyl, wherein R^5 is —OR^6, wherein R^6 is lower alkyl or hydrogen; X, Y, and Z are each —CH_2—; R^1 and R^3 are each hydrogen; R and R^2 are each —OR^6, wherein R^6 is hydrogen; and the sum of m, n, p, q and r is 2, 3 or 4.

8. A method of claim 6 wherein the HMG CoA reductase inhibitor is selected from the group consisting of lovastatin, pravastatin, fluvastatin, simvastatin and atorvastatin.

9. A method of claim 6 wherein the compound of formula I is selected from the group consisting of

rel 3(R)-(2(R)-hydroxy-2-phenylethyl)-4(R)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

rel 3(R)-(2(R)-hydroxy-2-phenylethyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

3(S)-(1(S)-hydroxy-3-phenylpropyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

3(S)-(1(R)-hydroxy-3-phenylpropyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

3(R)-(1(R)-hydroxy-3-phenylpropyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

3(R)-(3(R)-hydroxy-3-phenylpropyl)-1,4(S)-bis-(4-methoxyphenyl)-2-azetidinone;

3(R)-(3(S)-hydroxy-3-phenylpropyl)-1,4(S)-bis-(4-methoxyphenyl)-2-azetidinone;

4(S)-(4-hydroxyphenyl)-3(R)-(3(R)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone;

4(S)-(4-hydroxyphenyl)-3(R)-(3(S)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone;

rel 3(R)-[3(RS)-hydroxy-3-[4-(methoxymethoxy)-phenyl]propyl]-1,4(S)-bis-(4-methoxyphenyl)-2-azetidinone;

1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl)]-4(S)-(4-hydroxyphenyl)-2-azetidinone;

1-(4-fluorophenyl)-3(R)-[3(R)-(4-fluorophenyl)-3-hydroxypropyl)]-4(S)-(4-hydroxyphenyl)-2-azetidinone;

4(S)-[4-(acetyloxy)phenyl]-3(R)-(3(R)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone;

4(S)-[4-(acetyloxy)phenyl]-3(R)-(3(S)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone;

1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl)]-4(S)-[4-(phenylmethoxy)phenyl]-2-azetidinone;

3(R)-[3(R)-acetyloxy)-3-phenylpropyl]-1,4(S)-bis-(4-methoxy-phenyl)-2-azetidinone;

3(R)-[3(S)-acetyloxy)-3-phenylpropyl]-1,4(S)-bis-(4-methoxy-phenyl)-2-azetidinone;

3(R)-[3(R)-(acetyloxy)-3-(4-fluorophenyl)propyl]-4(S)-[4-(acetyloxy)-phenyl]-1 -(4-fluorophenyl)-2-azetidinone;

3(R)-[3(S)-(acetyloxy)-3-(4-fluorophenyl)propyl]-4(S)-[4-(acetyloxy)-phenyl]-1-(4-fluorophenyl)-2-azetidinone;

3(R)-[3(R)-(acetyloxy)-3-(4-chlorophenyl)propyl]-4(S)-[4-(acetyloxy)phenyl]-1-(4-chlorophenyl)-2-azetidinone;

3(R)-[3(S)-(acetyloxy)-3-(4-chlorophenyl)propyl]-4(S)-[4-(acetyloxy)phenyl]-1-(4-chlorophenyl)-2-azetidinone; and

rel 1-(4-fluorophenyl)-4(S)-(4-hydroxyphenyl)-3(R)-(1(R)-hydroxy-3-phenylpropyl)-2-azetidinone.

10. A method of claim 6 comprising administering a combination of 1-(4-fluorophenyl)-3(R)-[3(R)-(4-fluorophenyl)-3-hydroxypropyl)]-4(S)-(4-hydroxyphenyl)-2-azetidinone and lovastatin, pravastatin, fluvastatin, simvastatin or atorvastatin.

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